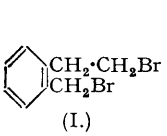
385. *The Synthesis and Properties of* 2 : 7-*Disubstituted* 1 : 2 : 3 : 4-*Tetrahydro*isoquinolines.

By M. H. Beeby and Frederick G. Mann.

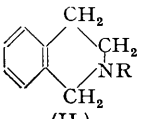
The synthesis of 5-*nitro*-2-2′-*chloroethylbenzyl chloride* by the chloromethylation of 2-*p*-nitrophenylethyl chloride, and the parallel synthesis of 5-*nitro*-2-2′-*bromoethylbenzyl bromide* are described. These compounds condense readily with primary amines to give the corresponding 7-nitro-2-aryl(or -alkyl)-1 : 2 : 3 : 4-tetrahydro*iso*quinolines. Reduction leads to the 7-amino-compounds, and other derivatives can thus be prepared.

It has been shown by Holliman and Mann (*J.*, 1942, 737) that *o*-2-bromoethylbenzyl bromide (I) can be obtained in a five-stage synthesis from *o*-toluidine, and is thus reasonably readily available. These workers showed also that the dibromide condensed readily with primary amines to give 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*quinolines (II) (*J.*, 1945, 34), and with sulphonamides to give the 2-sulphonyltetrahydro*iso*quinolines (III); furthermore the dibromide could

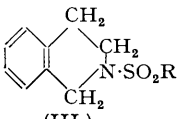
be condensed with alkyl (and aryl) dichloroarsines by the action of sodium to give the 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines (IV) (*J.*, 1943, 547). It is noteworthy however that none of the compounds of type (II), (III), or (IV) has any marked physiological activity. It appeared probable that the prime cause of this therapeutic inactivity was the absence of substituents in the *o*-phenylene ring.



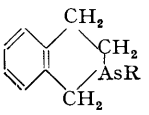
(I.)



(II.)

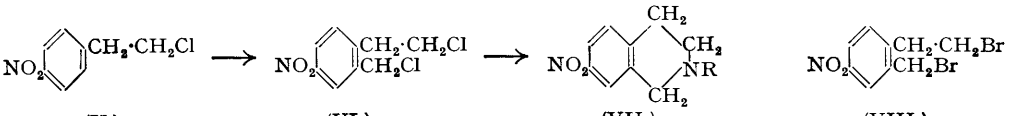


(III.)



(IV.)

The various stages in the above synthesis of the dibromide (I) preclude any practicable modification whereby a substituent could be introduced into the ring, and an entirely different synthetic route was thus required. For this purpose, therefore, 2-phenylethyl alcohol was converted into the chloride, which on nitration furnished 2-*p*-nitrophenylethyl chloride (V).



(V.) (VI.) (VII.) (VIII.)

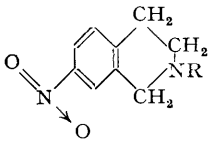
When treated with *s*-dichlorodimethyl ether in the presence of fuming sulphuric acid, (V) underwent smooth chloromethylation to give the crystalline *5-nitro-2-2′-chloroethylbenzyl chloride* (VI). The nature and position of the substituents in the compound (V) leave little doubt that the chloromethyl group has entered the position indicated in (VI), particularly as Stephen, Short, and Gladding (*J.*, 1920, **117**, 510) have proved that the chloromethylation of *p*-nitrotoluene gives 5-nitro-2-methylbenzyl chloride. The orientation of the substituents in the compound (VI) was, however, confirmed by the fact that this compound, when heated with various primary aryl amines and potassium carbonate in a suitable solvent, readily gave the corresponding 7-nitro-2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (VII), a condensation precisely similar to that given by the dibromide (I). For example, when the dichloride (VI) and *p*-toluidine in equimolecular quantities were boiled together in *n*-butyl alcohol in the presence of potassium carbonate, condensation occurred to form *7-nitro*-2-p-*tolyl*-1 : 2 : 3 : *4-tetrahydro*isoquinoline (VII; R = C_6H_4Me); this compound, when reduced in the presence of a platinum catalyst, gave the corresponding *7-amino*-2-p-*tolyltetrahydro*isoquinoline, which was converted in turn into the *7-acetamido*-, *7-benzamido*-, and *7-benzenesulphonamido*-derivatives. A similar mixture of the dichloride, 3 : 4-dimethoxyaniline hydrochloride, and potassium carbonate in boiling *n*-propyl alcohol gave *7-nitro*-2-(*3′* : *4′-dimethoxyphenyl*)-1 : 2 : 3 : *4-tetrahydro*isoquinoline [VII; R = $C_6H_3(OMe)_2$], which was similarly reduced to the *7-amino*-derivative.

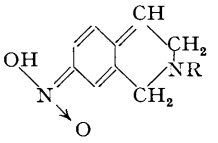
This condensation was not limited to arylamines. A mixture of the dichloride and *n*-butylamine in boiling ethyl alcohol gave ultimately 7-nitro-2-*n*-butyltetrahydro*iso*quinoline (VII; R = Bu^n) as the *hydrochloride*, and diethylaminoethylamine similarly gave 7-nitro-2-2′-diethylaminoethyltetrahydro*iso*quinoline (VII; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$) as the *dihydrochloride*.

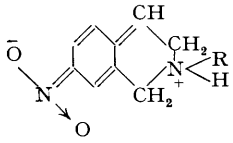
The use of the dichloride (VI) in these syntheses had however one disadvantage, inasmuch as efficient condensation with each primary amine investigated appeared to depend greatly on the temperature, and hence on the solvent, employed; consequently several solvents had to be tested for each amine before optimum conditions could be attained with reasonable certainty. To avoid this difficulty, the more reactive dibromide, corresponding to the dichloride (VI), was similarly prepared, 2-*p*-nitrophenylethyl bromide being treated with *s*-dibromodimethyl ether to give *5-nitro-2-2′-bromoethylbenzyl bromide* (VIII). This reacted readily with primary amines in boiling ethyl alcohol in the presence of potassium carbonate, and the use of solvents of higher b. p. now became unnecessary. Thus condensation under these conditions with *p*-chloroaniline gave *7-nitro*-2-p-*chlorophenyltetrahydro*isoquinoline (VII; R = C_6H_4Cl), which in turn furnished the *7-amino*- and the *7-acetamido*-derivatives, and condensation with *p*-aminoacetanilide gave *7-nitro*-2-p-*acetamidophenyltetrahydro*isoquinoline (VII; R = $C_6H_4{\cdot}NHAc$), which was also reduced to the *7-amino*-derivative.

In considering the constitution of the above compounds, it is noteworthy that all the 7-nitro-2-aryl(or -alkyl)-tetrahydro*iso*quinolines were coloured (yellow, orange, or red); this colour is clearly associated with the nitro-group, since all the corresponding 7-amino-compounds

were colourless. Furthermore, these coloured 7-nitrotetrahydro*iso*quinolines form colourless crystalline hydrochlorides. There are theoretically three possible structures for a 7-nitro-2-aryl(or -alkyl)-tetrahydro*iso*quinoline (VII). It might possess a normal nitro-group as in


(VII-A.)


(VII-B.)


(VII-C.)

(VII-A), or exist in the *aci*-form (VII-B), or the latter might give the zwitterion (VII-C). Now it is unlikely that the introduction of one normal nitro-group (VII-A) into the otherwise colourless tetrahydro*iso*quinoline would cause this marked development of colour. An interesting compound for direct comparison in this respect would be 7-nitro*iso*quinoline, where the nitro-group must retain its normal structure; this compound is apparently unknown, however, but 7-nitroquinoline, to which the same argument applies, is a colourless crystalline compound (Bacharach, Haut, and Caroline, *Rec. Trav. chim.*, 1933, **52**, 416). Moreover, if the 7-nitro-derivatives had the structure (VII-A), there is no obvious structural change that would accompany salt formation and cause the disappearance of the orange colour of the above.

It appears probable therefore that our 7-nitro-bases have the quinonoid structure (VII-B), or (VII-C), either of which would almost certainly be coloured, and that the presence of acids suppresses *aci*-formation, so that salts with strong acids (such as the hydrochloride) are salts of the normal form (VII-A). It would be expected that compounds having the highly polar structure (VII-C) would also have comparatively high m. p.s. The fact that both our 2-alkyl derivatives are mobile liquids which give no indication of crystallisation provides some evidence (although far from decisive) that they may have the less polar *aci*-structure (VII-B) rather than the zwitterion structure (VII-C).

The therapeutic activity of several of the above compounds is now being tested.

Experimental.

All the 7-substituted derivatives described below melted with preliminary darkening, the onset and degree of which depended on the particular compound concerned; the m.p.s were therefore determined in a preheated bath. All the 7-amino-compounds were unstable when exposed to light and air, usually rapidly developing a yellowish-brown coloration; the 7-acetamido-compounds behaved similarly, but the colour developed less rapidly.

Synthesis of 5-Nitro-2-2′-chloroethylbenzyl Chloride (VI).—(i) *2-Phenylethyl chloride.* This and the following compound were prepared by Barger (*J.*, 1909, **95**, 2193), who gave only brief details, particularly for the nitro-derivative; we have advantageously modified both preparations. 2-Phenylethyl alcohol (250 g.) was added over a period of 1 hour to a cold well-stirred mixture of phosphorus pentachloride (450 g.) and chloroform (1 l.), which was subsequently heated under reflux for 1·5 hours. The chloroform and most of the phosphorus oxychloride were then removed by distillation, and water was cautiously added to the cold residual liquid to hydrolyse the remaining oxychloride. The product was filtered under gentle suction to decrease emulsification and thus to obtain two well-defined layers. The chloride was separated, taken up in ether, thoroughly washed with water, dried (Na_2SO_4), and distilled; b. p. 112—116°/63 mm. Yield, 230—240 g.

The compound was also efficiently prepared by the action of thionyl chloride on the alcohol.

(ii) *2-p-Nitrophenylethyl chloride.* 2-Phenylethyl chloride (250 g.) was added dropwise during 1 hour to a well-stirred mixture of fuming nitric acid (400 c.c.) and concentrated nitric acid (300 c.c.), cooled in ice and water. The stirring was then continued for 5 hours without external cooling, and the reaction mixture poured into much ice–water and set aside overnight. The mixture of crystals and oil which separated was taken up in ether, and the solution washed with water and dried (Na_2SO_4), and the solvent removed. The yellow residual oil, when placed in a refrigerator overnight, deposited crystals of the *p*-nitro-compound, which were collected, washed with light petroleum, and thoroughly pressed between absorbent paper. The product thus obtained (105 g.) had m. p. 46—48° and, although still contaminated with traces of the *o*-nitro-isomer, was sufficiently pure for the next stage. The filtrate from the residual yellow oil was distilled *in vacuo*; the higher-boiling fraction crystallised on cooling, to yield a second crop of the *p*-nitro-compound; however, the average yield (20 g.) of this crop hardly justifies the time and labour expended.

(iii) *s-Dichlorodimethyl ether.* This was prepared essentially by the method of Descudé (*Bull. Soc. chim.*, 1906, **35**, 956), phosphorus trichloride (540 g.) being slowly added down a condenser to a vigorously agitated mixture of paraformaldehyde (540 g.) and zinc chloride (30 g.) in a 2-l. flask. When the vigorous reaction had subsided, the viscous mixture was distilled under reduced pressure until the temperature of the oil-bath reached *ca.* 140° and paraformaldehyde crystallised in the condenser. The crude distillate was sufficiently pure for the next stage.

The ether was more rapidly prepared by the method of Norris (*Ind. Eng. Chem.*, 1919, **11**, 817), but

the product on initial testing appeared to give much lower yields at the subsequent chloromethylation stage.

(iv) 5-*Nitro*-2-2′-*chloroethylbenzyl chloride*. 2-*p*-Nitrophenylethyl chloride (50 g.), crude dichlorodimethyl ether (100 g.), and fuming sulphuric acid (250 g., containing 20% of SO_3) were mixed, giving a homogeneous solution with heat evolution. This solution was heated on a water-bath for 3—5 minutes (further heating, which leads to considerable evolution of hydrogen chloride, must be avoided) and then set aside overnight. The solution was poured on ice, giving an oil which readily solidified. The crystals, when collected, washed with water and recrystallised from methyl alcohol or from light petroleum (b. p. 60—80°), gave the required *dichloride* as colourless crystals, m. p. 77° (Found : C, 46·5; H, 3·7; N, 5·7. $C_9H_9O_2NCl_2$ requires C, 46·15; H, 3·9; N, 6·0%); average yield, 41 g.

Synthesis of 5-*Nitro*-2-2′-*bromoethylbenzyl Bromide*.—(i) 2-p-*Nitrophenylethyl bromide*. This was prepared by nitration of 2-phenylethyl bromide as Foreman and McElvain (*J. Amer. Chem. Soc.*, 1940, **62**, 1436) describe.

(ii) s-*Dibromodimethyl ether*. This preparation was based essentially on the method of Tischtschenko and Rabcevitsch-Zubkovski (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 705). Bromine (435 g.) was added slowly during 4 hours to water (28 c.c.), to which a mixture of paraformaldehyde (150 g.) and red phosphorus (34 g.) was also added at a comparable rate, the reaction mixture being water-cooled meanwhile. The final product was set aside for 20 hours, and the heavy crude ether layer was then separated, saturated with hydrogen bromide, and dried (P_2O_5) for 1 day. Distillation gave the ether as a fraction of b. p. 146—159°, sufficiently pure for the following bromomethylation stage; yield, 320 g.

(iii) 5-*Nitro*-2-2′-*bromethylbenzyl bromide*. 2-*p*-Nitrophenylethyl bromide (75 g.), dibromodimethyl ether (225 g.), and fuming sulphuric acid (300 g., containing 20% of SO_3) were mixed, giving a homogeneous solution with heat evolution. This mixture was set aside for 48 hours and then poured on ice, a heavy reddish oil separating. The aqueous acid layer was decanted, and water was added to the reddish oil, which, when vigorously stirred and kneaded, ultimately solidified. The product, when collected, washed with water, drained, and recrystallised from alcohol, gave the required *dibromide* as colourless crystals, m. p. 92·5° (Found : C, 33·4; H, 2·9; N, 4·4. $C_9H_9O_2NBr_2$ requires C, 33·4; H, 2·8; N, 4·3%); yield, 58 g.

7-*Nitro*-2-p-*tolyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VII; R = C_6H_4Me).—(*a*) The dichloride (VI) (23·4 g.), *p*-toluidine (10·7 g., 1 mol.), anhydrous potassium carbonate (50 g.), and *n*-butyl alcohol (150 c.c.) were heated under reflux for 3 hours and then allowed to cool. The mixture was poured into water, and the orange solid which separated was collected, washed, and recrystallised from alcohol; the crude tetrahydro*iso*quinoline (16 g.; m. p. 92—95°) thus obtained, when twice recrystallised from *n*-hexane, gave orange needles, m. p. 96·5—98° (Found : C, 71·9; H, 6·0; N, 10·6. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%).

(*b*) The dibromide (VIII) (3 g.), *p*-toluidine (1 g., 1 mol.), potassium carbonate (4 g.), and alcohol (20 c.c.) were heated under reflux for 2·5 hours. The cold mixture was filtered, and the residue washed free from carbonate with water and then recrystallised from the filtrate with the addition of more alcohol. The tetrahydro*iso*quinoline thus obtained had m. p. 94—96°; yield, 1·75 g. (70%).

When an excess of alcoholic hydrogen chloride was added to a hot alcoholic solution of the above compound, the mixture immediately became colourless. Cooling and scratching ultimately caused the *hydrochloride* to separate in colourless crystals, melting at 194—195·5° to a red liquid which rapidly decomposed (Found : C, 62·5; H, 5·8. $C_{16}H_{16}O_2N_2$,HCl requires C, 63·0; H, 5·6%).

7-*Amino*-2-p-*tolyltetrahydro*isoquinoline.—The above nitro-base (9·6 g.) was suspended in alcohol (50 c.c.) containing platinum oxide (0·08 g.) and reduced by shaking at 50° with hydrogen at atmospheric pressure. When hydrogen absorption ceased, the solution was boiled, filtered, and cooled, the 7-*amino*-compound readily crystallising; a second crop (giving 6·75 g. in all) was obtained by concentration of the mother-liquor. Recrystallisation from light petroleum (b. p. 60—80°) (charcoal) gave the colourless amine, m. p. 87·5—88° (Found : C, 80·5; H, 7·9; N, 11·8. $C_{16}H_{18}N_2$ requires C, 80·6; H, 7·6; N, 11·8%). The following derivatives, prepared in the usual way, were all recrystallised from alcohol and obtained as colourless compounds : 7-*acetamido*-, m. p. 186—188° (Found : C, 77·0; H, 7·0; N, 10·2. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·2; N, 10·0%), 7-*benzamido*-, m. p. 156—158° (Found : C, 81·0; H, 6·7; N, 8·5. $C_{23}H_{22}ON_2$ requires C, 80·65; H, 6·5; N, 8·2%), 7-*benzenesulphonamido*-derivative, m. p. 160—165° (Found : C, 69·6; H, 5·7; N, 7·4. $C_{22}H_{22}O_2N_2S$ requires C, 69·8; H, 6·0; N, 7·4%).

3 : 4-*Dimethoxyaniline hydrochloride*. This was prepared from pyrocatechol by standard methods (Ullmann, *Annalen*, 1903, **327**, 115; Moureu, *Bull. Soc. chim.*, 1896, **15**, 647; Smith and Haller, *J. Amer. Chem. Soc.*, 1934, **56**, 237).

7-*Nitro*-2-(3′ : 4′-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline [VII; R = $C_6H_3(OMe)_2$].—A mixture of the dichloride (VI) (27·8 g.), 3 : 4-dimethoxyaniline hydrochloride (22·6 g., 1 mol.), potassium carbonate (60 g.), and *n*-propyl alcohol (200 c.c.) was heated under reflux for 2 hours and then filtered whilst hot. The filtrate on cooling deposited the 7-*nitro*-derivative (12·8 g.); the undissolved residue from the reaction mixture was digested with cold water, and a second crop (7·4 g.) thus obtained : total yield, 53%. The united crops, when recrystallised from alcohol, gave the pure 7-*nitro*-derivative as red crystals, m. p. 120—120·5° (Found : C, 64·75; H, 5·9; N, 9·2. $C_{17}H_{18}O_4N_2$ requires C, 64·9; H, 5·8; N, 8·9%).

This compound, when catalytically reduced as described above, gave the 7-*amino*-derivative in colourless crystals from alcohol, m. p. 144—144·5° (Found : C, 71·65; H, 6·9; N, 9·5. $C_{17}H_{20}O_2N_2$ requires C, 71·8; H, 7·1; N, 9·9%). The 7-*acetamido*-derivative also formed colourless crystals, m. p. 153—154°, from alcohol (Found : C, 70·1; H, 7·2; N, 8·65. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·8; N, 8·6%).

7-*Nitro*-2-n-*butyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline *Hydrochloride*.—A solution of the dichloride (VI) (4·16 g.) and *n*-butylamine (3·9 g., 3 mols.) in alcohol (20 c.c.) was heated under reflux for 30 minutes and then poured into water. The red oily *iso*quinoline which separated was extracted with ether, the solution dried (Na_2SO_4) and filtered, and the ether then removed. The residual red oil was dissolved in chloroform, which was then treated with hydrogen chloride. The crude *hydrochloride* (3·75 g.) which

separated was recrystallised from alcohol, giving colourless crystals, m. p. 224—226° (decomp.) (Found : C, 57·8; H, 7·0; N, 10·5. $C_{13}H_{18}O_2N_2$,HCl requires C, 57·4; H, 7·05; N, 10·3%).

7-*Nitro*-2-2′-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline *Dihydrochloride*.—This was prepared as the above compound, using the dichloride (VI) (16·8 g.), 2-diethylaminoethylamine (25·2 g., 3 mols.) and alcohol (120 c.c.). The red oil after removal of the ether was dissolved in acetone and treated with an acetone solution of hydrogen chloride. The precipitated *dihydrochloride* (22·3 g.), on recrystallisation from alcohol, gave colourless crystals, m. p. 232° (decomp.) (Found : C, 51·2; H, 7·45; N, 11·7. $C_{15}H_{23}O_2N_3$,2HCl requires C, 51·4; H, 7·2; N, 12·0%).

Catalytic reduction of this salt in alcohol gave the 7-*amino*-derivative *dihydrochloride*, as colourless crystals, m. p. 221—223° (decomp.), from alcohol (Found : C, 56·1; H, 8·25; N, 12·8. $C_{15}H_{25}N_3$,2HCl requires C, 56·2; H, 8·5; N, 13·1%). The 7-*acetamido*-derivative *dihydrochloride* also formed colourless crystals, m. p. 243—244° (decomp.), from alcohol (Found : C, 56·2; H, 8·0; N, 11·4. $C_{17}H_{27}ON_3$,2HCl requires C, 56·3; H, 8·1; N, 11·6%).

7-*Nitro*-2-p-*chlorophenyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VII; R = C_6H_4Cl).—A mixture of the dibromide (VIII) (12 g.), *p*-chloroaniline (7·2 g., 1 mol.), potassium carbonate, and alcohol (120 c.c.) was boiled under reflux for 2·5 hours and filtered whilst hot. The 7-*nitro*-compound separated as yellow crystals in the filtrate, and a further quantity was obtained by cold aqueous digestion of the residue from the initial filtration to remove potassium carbonate. The total product (6·8 g.) was recrystallised from alcohol, giving the pure yellow crystalline base, m. p. 130—131° (Found : C, 62·4; H, 4·8; N, 10·0. $C_{15}H_{13}O_2N_2Cl$ requires C, 62·4; H, 4·5; N, 9·7%). The *hydrochloride* was prepared precisely similarly to that of the 2-*p*-tolyl analogue; it formed colourless crystals, melting at 191—192° to a red liquid which rapidly decomposed (Found : C, 55·4; H, 4·6. $C_{15}H_{13}O_2N_2Cl$,HCl requires C, 55·4; H, 4·3%).

Catalytic reduction of this base was unsatisfactory; the base was therefore reduced using tin and hydrochloric acid in aqueous alcohol; the 7-*amino*-compound thus obtained formed colourless crystals, m. p. 107—108° (Found : C, 70·0; H, 6·0; N, 11·2. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·85; N, 10·8%). The 7-*acetamido*-compound also separated as colourless crystals, m. p. 171—172°, from alcohol (Found C, 68·2; H, 6·0; N, 9·4. $C_{17}H_{17}ON_2Cl$ requires C, 67·85; H, 5·7; N, 9·3%).

7-*Nitro*-2-p-*acetamidophenyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VII; R = C_6H_4·NHAc).—Prepared as the 2-*p*-chlorophenyl derivative, using the dibromide (VIII) (9 g.), *p*-aminoacetanilide (4·2 g., 1 mol.), potassium carbonate (12 g.), and alcohol (100 c.c.), and recrystallised from alcohol, the 7-*nitro*-compound formed yellow crystals, m. p. 216° (decomp.) (Found : C, 65·6; H, 5·8; N, 13·9. $C_{17}H_{17}O_3N_3$ requires C, 65·5; H, 5·5; N, 13·5%).

Catalytic reduction in alcohol gave the 7-*amino*-compound, colourless crystals, m. p. 159—160°, from alcohol (Found : C, 72·7; H, 7·1; N, 14·9. $C_{17}H_{19}ON_3$ requires C, 72·5; H, 6·8; N, 14·9%).

Several attempts were made to hydrolyse the above 7-nitro- and 7-amino-compounds with acids and with alkalis, and so to obtain the corresponding 2-*p*-aminophenyl derivatives, either as the free bases or at salts, but pure stable samples of these derivatives were not isolated.

We are indebted to Mr. H. Zeitlin, M.S., for assistance in the preliminary stages of this investigation carried out in the University of Hawaii with one of us (F. G. M.). We also gratefully acknowledge a grant from the Department of Scientific and Industrial Research (M. H. B.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 12th*, 1949.]