tion was separated, b. p. 97°, $n^{25}\mathrm{D}$ 1.4134, and identified as chloromethyltrimethylsilane. The acid-soluble portion was recovered b. p. 102°, $n^{25}\mathrm{D}$ 1.3904, and was apparently the ethyl ether. The third fraction was washed several times with water and dried over calcium chloride to yield a product (101 ml.) which was distilled b. p. 99–102°, $n^{25}\mathrm{D}$ 1.3972–1.3915, $d^{25}{}_4$ 0.798–0.761. An appreciable amount of chloride was present in this material. The last fraction obtained (30 ml.) was free of the chloride by qualitative tests and possessed the properties: b. p. 102° at 739 mm., $n^{25}\mathrm{D}$ 1.3915, $d^{25}{}_4$ 0.761. Calcd. for $Me_3SiCH_2OC_2H_5$: mol. refr.,[4] 41.31; mol. wt., 132. Found: mol. refr., 41.32; mol. wt. (Victor Meyer), 136. The other slightly lower boiling fractions were refluxed for several hours over sodium and redistilled, b. p. 103° at 751 mm., $n^{25}\mathrm{D}$ 1.3911, $d^{25}{}_4$ 0.755. *Anal.* Calcd. for $C_6H_{16}OSi$: Si, 21.2. Found: Si, 20.8, 20.9, 21.6; mol. refr., 41.61; mol. wt., 131. From distillation curves, density data on various fractions obtained, etc., the following approximate composition was arrived at in mole percentages: trimethylethoxysilane, 11%; unreacted chloromethyltrimethylsilane, 18%; ethoxymethyltrimethylsilane, 70%. The presence of no other silicon compounds was indicated.

The ethyl ether exploded with extreme violence when vaporized in a stream of oxygen, when analysis for carbon and hydrogen was attempted. The product did not give a positive test for peroxide, nor did its physical constants vary over a period of several weeks. It also exploded when mixed with sodium peroxide for fusion to determine the silicon content, but the silicon content could be determined by a wet combustion technique,[6] care being taken to avoid loss by volatilization during the early stages of the analysis.

Preparation of Butoxymethyltrimethylsilane.—The same procedure described for the preparation of the ethyl ether was followed using dry *n*-butanol in place of the ethanol. Distillation of the products revealed a small amount of material (5 cc.) b. p. 70°, containing no silicon which might be methoxybutane. The next fraction was unreacted chloromethyltrimethylsilane (13 ml., 9% of starting material), b. p. 92–102°. The third fraction (100 ml.) was identified as butoxytrimethylsilane–*n*-butanol azeotrope,[4] b. p. 111°, $n^{25}\mathrm{D}$ 1.394–1.398, corresponding to about a 31% yield of this product. (To confirm the identity of this fraction, a portion of it was heated to reflux for eight hours with a 100% excess of acetyl chloride to convert the butoxy silane to the corresponding chlorosilane and *n*-butyl acetate and the alcohol to the same ester, an easily separable mixture. The products were distilled and yielded only two fractions. The first was a mixture of acetyl chloride and trimethylchlorosilane, b. p. 49°, which yielded hexamethyldisiloxane on washing with water, b. p. 100°, $n^{25}\mathrm{D}$ 1.3750. The second fraction was *n*-butyl acetate, b. p. 125°, $d^{25}{}_4$ 0.881.) After most of the *n*-butanol, b. p. 116°, had been distilled from the reaction mixture, solids in the flask caused severe bumping. The distillation was interrupted and the material was washed with water, dried and the distillation was continued. The butyl ether was obtained (36 ml., 19%), b. p. 150° at 738 mm., $d^{25}{}_4$ 0.774, $n^{25}\mathrm{D}$ 1.4038. Calcd. for $C_8H_{20}OSi$: Si, 17.5; mol. refr.,[4] 50.67. Found: Si, 17.6, 17.1; mol. refr., 50.64.

The molecular weight of the compound could not be determined by the Victor Meyer method because the samples repeatedly exploded when vaporized in air. No qualitative test for peroxides was obtained from samples of the liquid, nor did its physical constants change on standing. A thick semi-solid non-volatile residue remained after the distillation. This residue contained silicon and was flammable, but was not identified.

The infrared absorption spectra of all three ethers prepared were very much alike, and revealed the strong maximum at 1100 cm.$^{-1}$ characteristic of alkyl ethers.

Summary

The synthesis of three new ethers, methoxymethyl-, ethoxymethyl- and butoxymethyltrimethylsilanes is reported, and the tendency of chloromethyltrimethylsilane to undergo hydrolytic cleavage under the influence of alcoholic sodium alkoxides was studied.

PITTSBURGH 13, PA. RECEIVED JULY 6, 1948

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[6] Speier, Daubert and McGregor, THIS JOURNAL, **70**, 1118 (1948).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Studies on the Willgerodt Reaction. VI. A Mechanism for the Primary Thiol Oxidation[1]

BY FREEMAN H. MCMILLAN[2] AND JOHN A. KING[2]

An earlier communication[3] from this Laboratory suggested a mechanism for the Willgerodt reaction which has seemed to account satisfactorily for all the known facts. At that time, as well as subsequently,[4] experimental data have been presented and pertinent contributory literature has been cited in support of the reactions postulated to occur intermediate to the starting material (A) and a primary thiol (B). Although a suggestion was also made concerning the conversion of the primary thiol (B) to an amide or thioamide (C), no supporting evidence was offered for this conversion. There have now been carried out experiments which enable us to draw definite conclusions regarding the mechanism of the transformation of B to C. These experiments and the interpretation of their results form the subject of the present paper.

$$\underset{\mathrm{A}}{RCOCH_3} \longrightarrow \underset{\mathrm{B}}{RCH_2CH_2SH} \longrightarrow \underset{\mathrm{C}}{RCH_2CSNR_2'}$$

Before proceeding directly with a discussion of these experiments, it is thought worthwhile to briefly consider a few other relevant points. It seems highly probable to us that the intrinsic mechanism of the reaction, as applied to aldehydes, ketones, alcohols, olefins, acetylenes and imines, is the same, whether it is carried out with aqueous ammonium polysulfide as originally done by Willgerodt or whether it is carried out with sulfur and an amine as was first used by Kindler; Stanek[5] has recently carried out the following reactions, by heating the material with three moles

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[1] For the preceding paper of this series see McMillan and King, THIS JOURNAL, **69**, 1207 (1947).

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[3] King and McMillan, THIS JOURNAL, **68**, 632 (1946).

[4] King and McMillan, *ibid.*, **68**, 1369 (1946).

[5] Stanek, *Collection Czechoslov. Chem. Commun.*, **12**, 671 (1947).

of sulfur followed by acid hydrolysis of the crude reaction product, and obtained the acids in the yields indicated: methylisobutylketoxime → isocaproic acid (10%); methylhexylketoxime → caprylic acid (10%); oximes of ketones lower than methyl butyl ketone → very poor yields; acetophenone oxime → phenylacetic acid (22%); acetophenone hydrazone and acetophenone azine → small quantity of very impure phenylacetic acid; acetophenone phenylhydrazone → phenylacetic acid (14%); we believe that these reactions likewise are adequately explained by the mechanism presented later in this paper, bearing in mind both the constant presence of hydrogen sulfide in any such reaction mixture and its ability to act as a reductant; for a literature review of the work published on this reaction through 1944, see Carmack and Spielman.[6]

This view of a common course for the various modifications of the reaction is shared by other workers[6,7] in the field who have stated "there must be one fundamental mechanism involving the preliminary formation of a labile intermediate which has an unsaturated carbon–carbon bond in the sidechain." As previously indicated, we believe that this unsaturated intermediate is an olefin obtained, from a ketone for example, *via* the possible sequence: ketone, thioketone, mercaptan, olefin, etc. Confirmation of our prediction concerning possible participation of thioketones in the reaction was recently obtained by Campaigne and Rutan[8] in their use of trithioacetophenone. Other results which we interpret as strong evidence for the intermediary formation of thioketones were obtained by Davis and Carmack[9] who found that several acrylic acids, $RCH{=}CHCOOH$ (or $RCH{=}C(CH_3)COOH$), underwent the reaction with loss of the original carboxyl carbon and conversion of the original α-carbon (or α-methyl) to a carboxyl; we consider this to proceed *via* 1,4-addition of hydrogen sulfide to the α,β-unsaturated acid to give, after tautomerization and oxidation of the $>CHSH$ to $>C{=}S$, a β-thioketo acid which undergoes decarboxylation in the normal manner[10] to a methyl thioketone $RCSCH_3$ that then is converted to RCH_2COOH (or $RCSCH_2CH_3$ to RCH_2CH_2COOH with the α-methyl derivative).

It further seems highly probable to us that the intrinsic mechanism is the same, whether the carbon chain is straight or branched; we cannot conclude that the same reaction, carried out under the same conditions, proceeds by different routes with such closely related compounds as, for example, propiophenone and isobutyrophenone, solely because somewhat lower yields are obtained with branched chain compounds and because cleavage may be more prevalent when the chain is branched. Instead of pointing to the existence of two different mechanisms, as was suggested by Carmack and DeTar,[7] we consider these variations in yield and extent of cleavage to be merely manifestations of the small inductive effect of the alkyl group on the sulfhydryl and hydroxyl groups and on the ethylenic bond as well as the larger result of steric factors. What we interpret as strong evidence for steric inhibition of the reaction was obtained from reactions carried out on isobutyrophenone. Under the same conditions as were used to convert propiophenone into β-phenylpropionic acid in 67% yield, isobutyrophenone was recovered unchanged to the extent of 89% and, in another run, 84% of the sulfur charged into the reaction mixture was recovered unchanged. If the first stages of the reaction had taken place and the progression of some functional group or unsaturation along the chain had been blocked by the branching in the chain the product isolated would have been derived from some intermediate or by-product of the reaction and could not possibly have been unchanged starting material.

Before a mechanism could be suggested for the conversion of B to C, it was necessary to learn what could conceivably occur under the reaction conditions used. It was found that at room temperature sulfur alone had no effect on a mercaptan. But if a trace of an amine (morpholine and *n*-butylamine were used) were added a spontaneous reaction occurred at room temperature, giving a good yield of disulfide according to the equation, which is written with a double arrow for reasons that will be discussed later in the paper.

$$2RCH_2SH + S \overset{\text{Catalyst}}{\rightleftarrows} RCH_2SSCH_2R + H_2S$$

The reaction, which proceeded smoothly and cleanly, was carried out on *n*-octyl mercaptan, benzyl mercaptan and β-phenethyl mercaptan. This is in agreement with the results of Holmberg,[11] who found that sulfur oxidized mercaptans to disulfides in aqueous 20% caustic. Therefore it is permissible to state that, starting with B, the above reaction can occur, in the conversion to C.

It was next found that a disulfide, with additional sulfur and with or without an amine catalyst, was unchanged at room temperature and at 200° either remained unchanged or merely gave polysulfides from which the disulfide could be recovered on distillation. Therefore the next step after the disulfide in the conversion of B to C must involve an amine molecule.

That an amine alone was not involved was shown by the fact that a disulfide and morpholine, heated together, underwent no reaction; the disulfide was recovered unchanged.

However, when a disulfide (dibenzyl and di-β-phenethyl disulfides were used), sulfur and mor-

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[6] Carmack and Spielman, "The Willgerodt Reaction," pp. 83–107, in Adams, "Organic Reactions," Volume III, John Wiley and Sons, Inc., New York, N. Y., 1946.

[7] Carmack and DeTar, THIS JOURNAL, **68**, 2029 (1946).

[8] Campaigne and Rutan, *ibid.*, **69**, 1211 (1947).

[9] Davis and Carmack, *J. Org. Chem.*, **12**, 76 (1947).

[10] Westheimer and Jones, THIS JOURNAL, **63**, 3283 (1941).

[11] Holmberg, *Ann.*, **359**, 81 (1908).

pholine all three were heated together there was obtained at least a 70% yield of thioamide in a fairly clean reaction (in the actual carrying out of the reaction an excess of morpholine was used in order to maintain fluidity of the reaction mixture and a much smaller excess of sulfur was used to replace that lost in the side reactions which always take place between sulfur and amines).

The results of this experiment merely confirmed the prediction that all three reactants were involved, but threw no light on additional intermediate stages. Therefore the same experiment was repeated, but with less reagents. One equivalent each of di-β-phenethyl disulfide and of sulfur heated with two equivalents of morpholine yielded a small amount of dithioöxalodimorpholide,[1,11a] some phenylacetaldehyde, and considerable unchanged disulfide. The same results were obtained when equimolar amounts of β-phenethyl mercaptan, sulfur and morpholine were heated together, indicating that the facile oxidation of the mercaptan to the disulfide is merely the preliminary stage in the conversion of the former to a carboxylic acid derivative. A very significant fact, however, is the isolation from these reactions of phenylacetaldehyde. The aldehyde was not present as such in the reaction mixture to an extent great enough to be detected by its odor, but when a benzene solution of the reaction mixture was washed with weakly acidified water the odor of the aldehyde became evident and the aldehyde itself was isolated and identified.

The phenylacetaldehyde could arise either from a side reaction or from an intermediate in the reaction to form the thioamide, in which case the intermediate would be a substance which on acid hydrolysis gives the aldehyde, and which on further oxidation gives a thioamide. These conditions are satisfied by an alkylidenediamine structure $RCH(NR_2')_2$, a type of substance which is known to be converted to an aldehyde by acid hydrolysis[12] and which has now been shown to be oxidized by sulfur to a thioamide. Thus, when the phenylmethylenediamine derived from benzaldehyde and morpholine was heated with sulfur, a 98% yield of thiobenzmorpholide was produced.

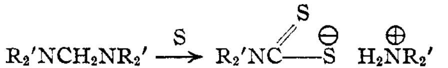
$$C_6H_5CH(NR_2')_2 + S \longrightarrow C_6H_5CSNR_2'$$

This may be considered as evidence in support of the premise that methylenediamines are involved in the conversion of a thiol to a thioamide, the complete sequence being

$$RCH_2SH \longrightarrow RCH_2SSCH_2R \longrightarrow RCH(NR_2')_2 \longrightarrow RCSNR_2'$$

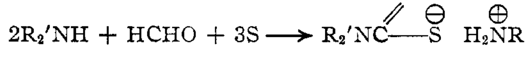
The methylenediamine hypothesis can also be used to explain the fact that acetophenone was isolated in 7% yield when styrene was treated with equimolar amounts of sulfur and morpholine, the ketone presumably being derived from the methylenediamine $C_6H_5C(CH_3)(NR_2')_2$.

The only previous studies related to the action of sulfur on a methylenediamine are those of Scott and Watt[13] who found that the formaldehyde derivative, methylene bis-(piperidine-1), gave on treatment with two moles of sulfur piperidinium piperidine-1-carbodithioate in 34% yield.



$$R_2'NCH_2NR_2' \xrightarrow{S} R_2'N\overset{\overset{S}{/\!/}}{C}-\overset{\ominus}{S}\quad H_2\overset{\oplus}{N}R_2'$$

When paraformaldehyde was treated with two equivalents of morpholine and three of sulfur, a crystalline product was produced which proved to be morpholinium morpholine-4-carbodithioate.



$$2R_2'NH + HCHO + 3S \longrightarrow R_2'N\overset{\overset{S}{/\!/}}{C}-\overset{\ominus}{S}\quad H_2\overset{\oplus}{N}R_2'$$

The yield was 74% based on the paraformaldehyde and the identity was established by comparison with an authentic sample,[14] as well as by comparison of the ester derived from it, methyl morpholine-4-carbodithioate, with an authentic sample.[15]

The same product was obtained when thioformylmorpholine was heated with an equivalent of sulfur.

$$R_2'NCHS \xrightarrow{S} R_2'N\overset{\overset{S}{/\!/}}{C}-\overset{\ominus}{S}\quad H_2\overset{\oplus}{N}R_2'$$

It was also found that piperidine, heated with paraformaldehyde and sulfur, gave piperidinium piperidine-1-carbodithioate,[13] although in poorer yield than was obtained in the corresponding reaction with morpholine.

Since Binz and Pence[16] found that piperidine or morpholine with aqueous formaldehyde and hydrogen sulfide at 55° gave piperidine-1-methanethiol or morpholine-4-methanethiol, respectively, and that piperidine-1-methanethiol on heating *in vacuo* gave methylene bis-(piperidine-1), it was of interest to study the action of sulfur on one of these simple methylenediamines.

When methylene bis-(morpholine-4) was heated with two moles of sulfur there was obtained a 46% yield of morpholinium morpholine-4-carbodithioate and the use of three moles of sulfur increased the yield to 70%; the reaction was spontaneous after the reactants had been heated to 150°. When the material was heated in a stream of hydrogen sulfide, morpholine was split out and 1,3-di-(4'-morpholino)-2-thiapropane was formed.

[11a] Horton and Van Den Berghe, THIS JOURNAL, **70**, 2425 (1948), have recently shown that dithioöxalodimorpholide is formed from sulfur and morpholine alone, and that its formation does not necessarily indicate degradation of some other substance.

[12] (a) Curtius and Davidis, *J. prakt. Chem.*, **54**, 66 (1896); (b) Curtius and Mott, *ibid.*, **94**, 323 (1916); (c) Curtius and Gund, *ibid.*, **107**, 177 (1924).

[13] Scott and Watt, *J. Org. Chem.*, **2**, 148 (1937).

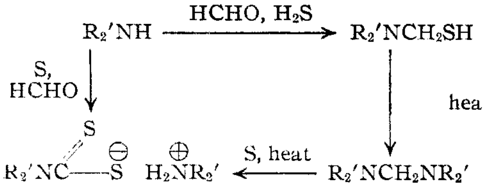
[14] Carter, U. S. Patent 2,369,893.

[15] Although the salt morpholinium morpholine-4-carbodithioate was described in Ref. 14 as a white solid, no properties were given. v. Braun, *Ber.*, **35**, 3368 (1902), showed that treatment of dithiocarbamate salts with alkyl halides produces alkyl esters of aminocarbodithioates (dithiourethans) which have characteristic melting points.

[16] Binz and Pence, THIS JOURNAL, **61**, 3134 (1939).

$$2R_2'NCH_2NR_2' + H_2S \longrightarrow 2R_2'NH + R_2'NCH_2SCH_2NR_2'$$

From the observations made in this Laboratory and from the information given in the papers cited, one can construct the reaction scheme



When equimolar amounts of morpholine-4-methanethiol and morpholine were heated with two moles of sulfur there was obtained, in a clean but slow reaction, a 72% yield of morpholinium morpholine-4-carbodithioate. We interpret this as indicating that, in this particular case, the slow stage is the reaction of the thiol and the amine to give the methylenediamine, because the latter reacted spontaneously with sulfur, at 150°, to give the carbodithioate.

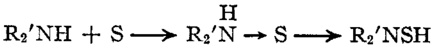
Theoretical Considerations.—Inasmuch as the Willgerodt reaction, including its several modifications, is as far as we are aware the only reaction known in organic chemistry in which a primary thiol undergoes ultimate oxidation to a carboxylic acid derivative, *i. e.*, oxidation of the carbon instead of only the sulfur, it seems worthwhile to seek an explanation of this unique conversion.

As indicated above, it appears to be well established that the first stage in the conversion is the base-catalyzed oxidation by sulfur of the mercaptan to a disulfide. Since neither sulfur alone nor

$$2\,RCH_2SH + S \rightleftarrows RCH_2SSCH_2R + H_2S \quad (I)$$

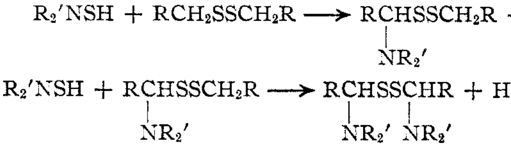
an amine alone had any action on a disulfide, one can only conclude that the next stage is either a trimolecular collision reaction, or that, more probably, a disulfide (A) is acted upon by some product derived from sulfur and the amine or (B) undergoes base-catalyzed oxidation by sulfur.

Although multifarious products have been obtained from the action of sulfur on various amines or ammonia these products generally are the result of some deep-seated reaction which irreversibly removes the amine from participation in any subsequent reaction. One must therefore, in the present case, seek a reaction which is either reversible or whose product in some manner can again be converted to the original amine. It is well known that the action of atomic oxygen (peroxides, peracids, etc.) on tertiary amines gives amine oxides; similar reactions have been carried out on less highly substituted amines to give less stable amine oxides which easily rearrange to hydroxylamines. An oxidation of this type might reasonably be expected to occur, although perhaps less easily, with atomic sulfur. The fact that an amine sulfide or a thiohydroxylamine has, as far as we are aware, not been prepared or isolated does not weaken the argument; derivatives of such compounds are known, such as the sulfenamides, *e. g.*, $C_6H_5NH-S-C_6H_5$, which can be considered as substituted thiohydroxylamines. It is therefore suggested that sulfur and the amine interact to form an



$$R_2'NH + S \longrightarrow R_2'\overset{H}{N} \rightarrow S \longrightarrow R_2'NSH \quad (II)$$

amine sulfide and that it is this product, either as such or more probably in its thiohydroxylamine form, which reacts with the disulfide. If this is the case, the next step would be a base-catalyzed condensation with the methylene group of the disulfide:

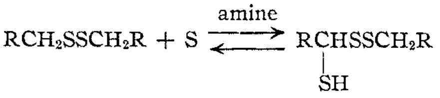


$$R_2'NSH + RCH_2SSCH_2R \longrightarrow \underset{NR_2'}{RCH}SSCH_2R + H_2S$$

$$R_2'NSH + \underset{NR_2'}{RCH}SSCH_2R \longrightarrow \underset{NR_2'}{RCH}SS\underset{NR_2'}{CHR} + H_2S \quad (III)$$

As pointed out by Woodward and Eastman[17] the sulfur atom in the system $-S\overset{|}{C}H-$ is considered to have a considerable proton-releasing effect on the attached carbon atom, possibly due to anion stabilization through such forms as $-\overset{\ominus}{S}{=}\overset{|}{C}-$. This involves the assumption that the valence shell of sulfur can accommodate more than eight electrons; compare references 16, 17, 18 cited by Woodward and Eastman; in a more recent study, involving the ultraviolet absorption spectra of sulfur compounds, Fehnel and Carmack[18] consider the expansion of the sulfur valence shell to a decet as a possible explanation of their results.

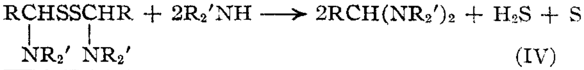
In alternative (B), in which the disulfide undergoes base-catalyzed oxidation by sulfur, one must assume that the oxidation is reversible and that the point of equilibrium is far to the left because



$$RCH_2SSCH_2R + S \overset{\text{amine}}{\rightleftarrows} \underset{SH}{RCH}SSCH_2R$$

it was demonstrated that disulfides are unchanged by sulfur in the presence of catalytic amounts of amines. The oxidation product, if formed, would have a carbon atom in the aldehyde state of oxidation and would be expected to condense with an amine to give the same product as obtained by the thiohydroxylamine mechanism. Because disulfides are unattacked by sulfur in the presence of amine catalyst whereas amines do react with sulfur, we prefer alternative (A).

Reaction of the diaminodisulfide, attained by either mechanism (A) or (B), with additional amine, could yield the alkylidenediamine structure, the evidence for which has been presented above.



$$\underset{NR_2'}{RCH}SS\underset{NR_2'}{CHR} + 2R_2'NH \longrightarrow 2RCH(NR_2')_2 + H_2S + S \quad (IV)$$

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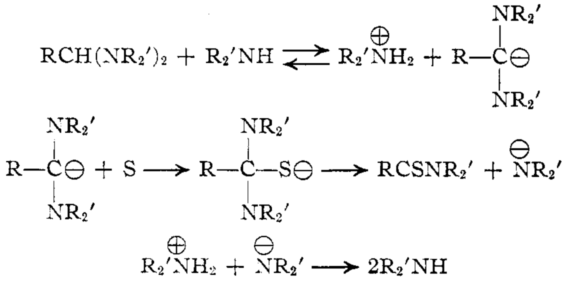
[17] Woodward and Eastman, THIS JOURNAL, 68, 2229 (1946).

[18] Fehnel and Carmack, paper 62 presented before the Division of Organic Chemistry, 113th meeting of American Chemical Society, Chicago, Illinois, April 21, 1948. Abstracts of meeting, p. 51L.

It is not unreasonable to assume that in the alkylidenediamine the –I effect (electron attraction) of the two amino groups gives rise, in its ultimate effect, to increased proton release at the central carbon atom. As a result the hydrogen is loosely bound and becomes, electronically speaking, acidic enough that it can be removed, by an amine molecule, sufficiently far from the carbon atom to allow the latter to become anionic. This removal may be facilitated by the possible existence of resonance in the ion produced. The oxidizing agent, elemental sulfur, acts upon this anion to give a diaminothiol ion that stabilizes itself by expulsion of an amino group and is thereby converted to a thioamide molecule. The expelled amino group is neutralized by the ammonium ion formed in the first step of the change to give two neutral amine molecules. Actually, of course, these four steps are occurring simultaneously: as an amine molecule is abstracting the proton from one side of the molecule the sulfur is approaching from the opposite side and the amino group is being expelled and also being neutralized by the ammonium ion. The net result of these steps is merely the oxidation of an alkylidenediamine to a thioamide by a sulfur atom, with liberation of an amine molecule, all in one smooth change.



$$\mathrm{RCH(NR_2')_2 + R_2'NH \rightleftharpoons R_2'\overset{\oplus}{N}H_2 + R{-}\underset{NR_2'}{\overset{NR_2'}{C}}\ominus}$$

$$\mathrm{R{-}\underset{NR_2'}{\overset{NR_2'}{C}}\ominus + S \longrightarrow R{-}\underset{NR_2'}{\overset{NR_2'}{C}}{-}S\ominus \longrightarrow RCSNR_2' + \overset{\ominus}{N}R_2'}$$

$$\mathrm{R_2'\overset{\oplus}{N}H_2 + \overset{\ominus}{N}R_2' \longrightarrow 2R_2'NH}$$

$$\mathrm{RCH(NR_2')_2 + S \longrightarrow RCSNR_2' + HNR_2'} \quad \text{(V)}$$

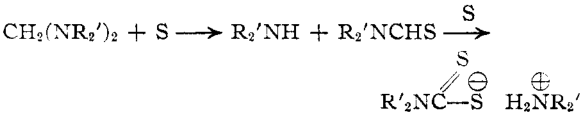
It is obvious, of course, that this oxidation cannot obtain with the intermediates derived from or via secondary and tertiary mercaptans. Considering the latter first, because equations (III), (IV) and (V) require an hydrogen on the carbon adjoining the sulfur atom one is left with equation (I) the oxidation to a disulfide, as the only step applicable to tertiary mercaptans. And, if one excludes ultimate reduction to an hydrocarbon (which was previously shown by us to be the case with pivalophenone if conditions were sufficiently drastic) as the only alternative, one must also conclude that this step is reversible; otherwise the di-*t*-disulfide would be the end-product isolated from reactions carried out on such compounds as isobutyrophenone; for specific examples of the relative inertness toward oxidation of di-*t*-disulfides see Small, Bailey and Cavallito.[19] Hence whatever tertiary mercaptan does undergo step (I) must also undergo reversal of this step followed by loss of hydrogen sulfide and readdition of the –SH to a carbon adjacent to the tertiary carbon, in order to actively participate in the conversion of the starting material into a carboxylic acid derivative of the same carbon content. A probably slight but still positive factor in regard to step (I) is the fact that, by virtue of their inherent structure, primary mercaptans will undergo this step more easily than will secondary mercaptans which in turn will react more easily than tertiary mercaptans. The same reasoning can, but need not necessarily, be applied to secondary mercaptans. These can undergo steps I–IV but the diamine $R_2C(NR_2')_2$ cannot undergo further oxidation without rupture of a carbon–carbon linkage; such a rupture is an alternative to our earlier suggestion of 2,3-scission of a 1,4-diradical; should it occur the more positive of the R radicals would be expelled as a carbonium ion, the rest of the sequence being the same as indicated for $RCH(NR_2')_2$. We believe that a diamine $R_2C(NR_2')_2$ can undergo a "thiohydrolytic" type of reaction with hydrogen sulfide

$$\mathrm{R_2C(NR_2')_2 + H_2S \longrightarrow HNR_2' + R_2C(SH)NR_2'}$$

$$\mathrm{R_2C(SH)NR_2' \longrightarrow HNR_2' + R_2C{=}S}$$

and thereby be reconverted to a thioketone which can again participate in the equilibria; the "thiohydrolysis" of methylene bis-(morpholine-4), herein reported, is considered as evidence for the possibility of this reaction.

When R is H, in equations I–IV, the same oxidation of step V can be repeated to yield, under anhydrous conditions, the dithiocarbamate (carbodithioate) which is the oxidation product actually isolated.



$$\mathrm{CH_2(NR_2')_2 + S \longrightarrow R_2'NH + R_2'NCHS \xrightarrow{S} R'_2N\overset{\overset{S}{\|}}{C}{-}\overset{\ominus}{S}\quad H_2\overset{\oplus}{N}R_2'}$$

Summation of equations I–V shows that, according to the proposed mechanism, the over-all equation for the oxidation of a primary thiol to a thioamide should be

$$\mathrm{RCH_2SH + R_2'NH + 2S \longrightarrow RCSNR_2' + 2H_2S}$$

which is in agreement with the experimental observations. In the aqueous ammonia procedure, where R′ is H and water is present, the thioamide formed will be hydrolyzed to an amide, with the accompanying acid produced by gradual hydrolysis of the amide. This is a departure from our earlier view and is in agreement with the conclusions of Carmack and DeTar,[7] who originally suggested that thioamides were also first formed in the aqueous reaction mixtures.

The above mechanism affords a satisfactory explanation of all of our experimental data and constitutes the only reaction mechanism ever proposed for the oxidation of a primary thiol to a carboxylic acid derivative.

It is recognized that a statement of Dauben,

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(19) Small, Bailey and Cavallito, THIS JOURNAL, **69**, 1710 (1947).

Reid, Yankwich and Calvin[20] contradicts the view that acids are formed by hydrolysis of amides in the Willgerodt reaction. Both Shantz and Rittenberg,[21] using C^{13} in the carbonyl group, and Dauben, *et al.*, using C^{14} in the carbonyl group, agreed that when the reaction was carried out on acetophenone the amide (or thioamide) was formed with non-rearrangement of the carbon chain. Dauben, *et al.*, however, stated that from the mother liquors of the amide there was obtained, in *ca.* 14% yield, a crude acid, containing amide, and that this residue in the mother liquor from the pure amide on hydrolysis gave phenylacetic acid which contained 75% of the initial specific activity in the carboxyl group. It will be instructive to see the complete experimental details upon which their Communication to the Editor was based. If rigorous proof of the presence of appreciable amounts of C^{14} in the carboxyl group of the phenylacetic acid is provided, then we must agree that the acid and amide are not formed by the same mechanism.

This constitutes our final contribution on this subject. We wish to express our appreciation to Dr. C. M. Suter for his continued interest in the work.

Experimental Part[22,23]

β-Phenylpropionic Acid from Propiophenone.—A mixture of propiophenone (67 g., 0.50 mole), morpholine (87 g., 1.00 mole) and sulfur (40 g., 1.25 mole) was refluxed for two hours. The cooled mixture was taken up in chloroform (250 cc.) and this solution was washed successively with water, dilute hydrochloric acid, and water. The chloroform was removed under vacuum and the residue was refluxed for eight hours with 500 g. of 50% (by weight) sulfuric acid. The cooled hydrolysis mixture was extracted three times with 150-cc. portions of ether and the combined ethereal extract was washed with 500 cc. of 5% sodium hydroxide. The alkaline wash was acidified and then extracted three times with 100-cc. portions of ether. Removal of the solvent from the dried extract left 50 g. (67% yield) of β-phenylpropionic acid, m. p. 46.5–47.5°.[24]

The same reaction was carried out on a mixture of isobutyrophenone (49.3 g., 0.33 mole), morpholine (58 g., 0.83 mole) and sulfur (26.7 g., 0.67 mole). The combined ethereal extract of the hydrolysis mixture, after the caustic wash, was dried and the solvent was removed to leave 47 g. of mobile liquid. On distillation at atmospheric pressure there was obtained 44 g. (89% recovery) boiling at 200–215° (mostly at 210°) which on redistillation under vacuum gave 38 g., b. p. 102° (20 mm.). This material gave a dinitrophenylhydrazone, m. p. 161–162.5°, undepressed when mixed with an authentic sample of the dinitrophenylhydrazone of isobutyrophenone.[25] The above mentioned caustic-wash was worked up to give 0.9 g. (1.6% yield) of acidic material, which, because of small amount, was not investigated further.

From a similar experiment in which the sulfuric acid hydrolysis was omitted there was obtained, on direct distillation, 39 g. (79% recovery) of isobutyrophenone, b. p. 105° (22 mm.) and, by filtration, 22.5 g. (84% recovery) of sulfur.

Di-β-phenethyl Disulfide.—A mixture of β-phenethyl mercaptan (69 g., 0.50 mole) and an amine (1 cc. of either morpholine or *n*-butylamine) was stirred at room temperature as sulfur (10 g., 0.31 mole) was added portionwise, accompanied by vigorous evolution of hydrogen sulfide. The solution was stirred for one hour after the addition was completed and then was allowed to stand overnight. The mixture was taken up in benzene (100 cc.), a small amount of sulfur was removed by filtration, and the benzene solution was washed successively with water, dilute hydrochloric acid, dilute sodium hydroxide and water. After removal of the benzene the residue was fractionally distilled through a six-inch helices-packed column to give 11 g. (16% recovery) of unchanged thiol, b. p. 55–59° (1 mm.) and 49 g. (71% yield) of disulfide, b. p. 168–180° (1.5 mm.). On redistillation the disulfide boiled at 172–175° (0.8 mm.).[26]

A similar procedure with *n*-octanethiol gave an 80% yield of **di-*n*-octyl-disulfide,** b. p. 160–163° (1.5 mm.).[27]

Benzyl mercaptan was similarly oxidized but when the reaction was over the mixture set to a solid mass. After two recrystallizations from ethanol there was obtained an 89.5% yield of **dibenzyl disulfide,**[28] m. p. 70–71.5°.

Willgerodt Reaction on Di-β-phenethyl Disulfide.—A mixture of di-β-phenethyl disulfide (2.74 g., 0.01 mole), morpholine (3.48 g., 0.04 mole) and sulfur (1.28 g., 0.04 mole) was refluxed for one hour and then worked up in the usual manner. The reaction product, after five hours of hydrolysis, and processing in the usual manner, furnished 1.90 g. (70% yield) of phenylacetic acid, m. p. 73–75°.

A similar type of experiment, using dibenzyl disulfide, gave **thiobenzmorpholide,** m. p. 137.5–138.5° after recrystallization from absolute alcohol.

Anal. Calcd. for $C_{11}H_{13}NOS$: N, 6.76. Found: N, 6.64.

A mixture of di-β-phenethyl disulfide (5.48 g., 0.02 mole), morpholine (3.48 g., 0.04 mole) and sulfur (0.64 g., 0.02 mole) was refluxed for two hours. The cooled reaction mixture was taken up in benzene (50 cc.) and washed successively with water, dilute hydrochloric acid and water. There was a distinct odor of phenylacetaldehyde at this point. The benzene was removed under vacuum and the residue was subjected to steam distillation, about 100 cc. of distillate being taken. The distillate was extracted twice with 25-cc. portions of ether, the combined extract was dried and the solvent was removed to leave 0.3 g. of oil which was converted to a semicarbazone by the usual procedure. After recrystallization from aqueous alcohol the material melted at 152–154°, undepressed when mixed with an authentic sample of the semicarbazone of phenylacetaldehyde. The water was removed from the steam distillation residue and the remaining dark residue was mixed with an equal volume of Skellysolve B. Everything dissolved except about 0.2 g. of material, which, after recrystallization from absolute alcohol, melted at 250–254°, undepressed when mixed with an authentic sample of dithioöxalodimorpholide.[1]

When a mixture of β-phenethyl mercaptan (20.7 g., 0.15 mole), morpholine (13.1 g., 0.15 mole) and sulfur (4.8 g., 0.15 mole) was refluxed for four hours and then worked up as described in the preceding paragraph there

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[20] Dauben, Reid, Yankwich and Calvin, THIS JOURNAL, **68,** 2117 (1946). Also paper 52 presented before the Division of Organic Chemistry at the 113th meeting of the American Chemical Society, Chicago, Illinois, April 21, 1948.

[21] Shantz and Rittenberg, THIS JOURNAL, **68,** 2109 (1946).

[22] Melting points and boiling points are uncorrected.

[23] Analytical determinations were carried out in the Analytical Laboratories of this Institute.

[24] This same reaction was reported by Schwenk and Papa, *J. Org. Chem.*, **11,** 798 (1946), but is recapitulated here for the purpose of comparison with the corresponding reactions with isobutyrophenone.

[25] Evans, *J. Chem. Soc.*, 785 (1936).

[26] Holmberg, *Ark. Kemi, Minerol. Geol.*, **12A,** No. 14, 10 (1937), prepared this disulfide by iodine oxidation of the thiol and reported that the compound could not be crystallized but said nothing about distillation of it. v. Braun, *Ber.*, **45,** 1565 (1912), prepared it by bromine oxidation of the thiol and reported that it could not be distilled without decomposition but did not mention the pressure at which distillation was attempted.

[27] Westlake and Dougherty, THIS JOURNAL, **64,** 149 (1942).

[28] Fromm and Schmoldt, *Ber.*, **40,** 2870 (1907).

was obtained 1.5 g. of oil which gave the semicarbazone of phenylacetaldehyde, m. p. 153–155° alone or when mixed with an authentic sample and about 1 g. of dithiooxalodimorpholide, m. p. 251–252° alone or when mixed with an authentic sample.

Thiobenzmorpholide.—An intimate mixture of finely divided α,α-bis-(morpholinyl-4)-toluene[29] (13.1 g., 0.05 mole) and sulfur (1.6 g., 0.05 mole) was heated to 145°, at which point a spontaneous reaction occurred. The reaction mixture solidified on cooling. The mass was broken up and triturated with Skellysolve A, then the solid was removed by filtration. The product weighed 10.1 g. (98% yield) and melted at 134.5–136°, undepressed when mixed with the sample of thiobenzmorpholide prepared from dibenzyl disulfide.

Acetophenone from Styrene.—A mixture of styrene (15.6 g., 0.15 mole), morpholine (13.1 g., 0.15 mole) and sulfur (4.8 g., 0.15 mole) was refluxed for two and one-half hours. The cooled reaction mixture smelled strongly of styrene. The mixture was taken up in benzene (100 cc.) and the solution was washed successively with water, dilute hydrochloric acid, and water. The benzene was removed under vacuum and the residue was subjected to steam distillation, about 200 cc. of distillate being taken. The distillate was extracted with 50-cc. portions of ether, the combined extract was dried and the solvent was removed to leave about 1 g. of residual oil. This oil gave a semicarbazone, m. p. 198–199° after recrystallization from 95% alcohol. There was no depression of the melting point when this material was mixed with an authentic sample of acetophenone semicarbazone.

The oil remaining in the steam distillation residue crystallized on cooling. After being washed with Skellysolve B it weighed 9.5 g. (29% yield) and melted at 71–77°. After one recrystallization from alcohol it melted at 77–78°, undepressed when mixed with an authentic sample of phenylthioacetmorpholide.

Morpholinium Morpholine-4-carbodithioate (from Paraformaldehyde).—A mixture of paraformaldehyde (6.0 g., 0.20 mole), morpholine (17.4 g., 0.20 mole) and sulfur (12.8 g., 0.40 mole) was refluxed (air condenser) for five hours, during which considerable crystallization occurred within the reaction mixture. The flask was cooled, its contents were boiled with benzene (150 cc.), and the solid was removed by filtration. The dry solid weighed 10.4 g. (21% yield, based upon the paraformaldehyde).

Anal. Calcd. for $C_9H_{18}N_2O_2S_2$: N, 11.20; S, 25.60. Found: N, 11.00; S, 25.28.

The material was a crystalline solid which sublimed without melting, could be recrystallized from methanol or from a large volume of benzene, and was very soluble in water to give a solution which had an odor of carbon disulfide. When the reaction was repeated using paraformaldehyde (6.0 g., 1.20 mole), morpholine (34.8 g., 0.40 mole) and sulfur (12.8 g., 0.40 mole) the yield of product was 19.3 g. (39% yield, based upon the paraformaldehyde).

The use, under the same conditions, of paraformaldehyde (6.0 g., 0.20 mole), morpholine (34.8 g., 0.40 mole) and sulfur (19.2 g., 0.60 mole) gave 37.0 g. of product (74% yield, based upon the paraformaldehyde).

Morpholinium morpholine-4-carbodithioate (0.50 g., 0.002 mole) was dissolved in water (15 cc.) and a solution of lead acetate (0.65 g., 0.002 mole) in water was added. The mixture was stirred for several minutes and then filtered. The filter cake was thoroughly washed with water and then dried, after which it gave a fairly satisfactory analysis for the lead salt of morpholine-4-carbodithioic acid.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S_4Pb$: Pb, 39.0. Found: Pb, 39.8.

The filtrate from which the lead salt had been removed was acidified with concentrated hydrochloric acid (5 cc.) and taken to dryness under vacuum. The residue was boiled with absolute alcohol and filtered. The alcoholic filtrate was taken to dryness to leave 0.19 g. of morpholine hydrochloride (m. p. 172–175°) which after recrystallization from absolute alcohol (1 cc.) melted at 174–176°, undepressed when mixed with an authentic sample.

Methyl Morpholine-4-carbodithioate.—To a suspension of morpholinium morpholine-4-carbodithioate (2.50 g., 0.01 mole) in methanol (25 cc.) there was added methyl iodide (1.42 g., 0.01 mole). The mixture was allowed to stand with occasional swirling for four hours, at the end of which time there was a clear solution, and was then poured into water (200 cc.). The crystalline solid removed by filtration weighed 1.00 g. (56% yield) and melted at 82.5–83.5° after two recrystallizations from aqueous methanol.

Anal. Calcd. for $C_6H_{11}NOS_2$: N, 7.91. Found: N, 7.88.

Morpholinium Morpholine-4-carbodithioate (from Carbon Disulfide).[14]—To a cooled and stirred solution of morpholine (34.8 g., 0.40 mole) in ethanol (100 cc.) there was added a solution of carbon disulfide (15.2 g., 0.20 mole) in ethanol (100 cc.). The suspension was stirred for thirty minutes and then filtered to give 48.0 g. (96% yield) of white solid which sublimed without melting.

Some of this material was converted to the methyl ester, as described above to give a product, m. p. 82.5–83.5°. The melting point of this material was not depressed on admixture either with the above ester or with methyl esters prepared from any of the samples of morpholinium morpholine-4-carbodithioate whose preparation is described in this paper.

Morpholinium Morpholine-4-carbodithioate (from Thioformylmorpholine).—A finely ground mixture of thioformylmorpholine[1] (2.62 g., 0.02 mole) and sulfur (0.64 g., 0.02 mole) was heated to 220° and then allowed to cool. The reaction mixture was boiled with benzene (100 cc.) and the product was removed by filtration. It weighed 1.2 g. (46% yield) and was identical with other samples of the same material.

Methylene-bis-(morpholine-4).—This material was prepared by the procedure of Harradence and Lions.[30]

Morpholinium Morpholine-4-carbodithioate (from Methylene-bis-(morpholine-4)).—In a 100-cc. round-bottomed flask was placed a mixture of methylene-bis-(morpholine-4) (18.6 g., 0.10 mole) and sulfur (6.4 g., 0.20 mole). The flask was fitted with an air condenser and was then heated in an oil-bath to 150°, at which temperature a vigorous reaction set in and heating was stopped. When the flask had cooled, it and the condenser were washed out with methanol and the almost white crystalline solid was removed by filtration. The product weighed 11.5 g. (46% yield).

When the same reaction was repeated using methylene-bis-(morpholine-4) (18.6 g., 0.10 mole) and sulfur (9.6 g., 0.30 mole) the yield of product was 17.5 g. (70% yield).

Hydrogen Sulfide Cleavage of Methylene-bis-(morpholine-4).—In a 250-cc. three-necked round-bottomed flask there was placed methylene-bis-(morpholine-4) (18.6 g., 0.10 mole). The flask was fitted with a gas inlet tube, a thermometer and a still head with downward air condenser. The flask was heated to 165° and a moderate stream of hydrogen sulfide was passed in for one and one-half hours. About 3 g. of distillate came over during this time, at a head temperature of 75–90°. On redistillation this material boiled at 123–127° and gave a hydrochloride melting at 174–176°, undepressed when mixed with an authentic sample of morpholine hydrochloride.

The pot residue from the reaction was allowed to stand overnight, giving crystals which were removed by filtration. They melted at 94–102° and weighed 4.5 g. (39% yield). After two recrystallizations from acetone the material melted at 106.5–108°, undepressed when mixed with an authentic sample of bis-(4-morpholinyl)-methyl sulfide prepared by the procedure of Binz and Pence.[16]

Morpholine-4-methanethiol.—This material was prepared by the procedure of Binz and Pence.[16]

Morpholinium Morpholine-4-carbodithioate (from Morpholine-4-methanethiol).—A mixture of morpholine-4-methanethiol (1.33 g., 0.01 mole), morpholine (0.87 g.,

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(29) Zief and Mason, *J. Org. Chem.*, **8**, 1 (1943).

(30) Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 22 (1939); *C. A.*, **33**, 7799 (1939).

0.01 mole) and sulfur (0.64 g., 0.02 mole) was heated at 160° for one hour. The contents of the flask was boiled with benzene (50 cc.) and the solid was removed by filtration. The product weighed 1.80 g. (72% yield) and was quite pure as indicated by almost quantitative recovery on sublimation.

Summary

A detailed reaction mechanism has been suggested for the conversion, in the Willgerodt reaction, of a primary thiol to a carboxylic acid derivative. Experimental data have been presented in support of the mechanism and various interrelationships between the reaction intermediates have been demonstrated.

Rensselaer, New York Received May 5, 1948

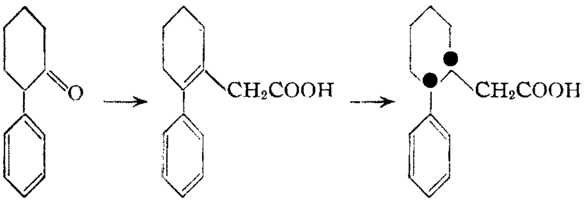
[Contribution from the Department of Chemistry, Washington University]

The Stereochemistry of the 2-Phenylcyclohexanecarboxylic Acids and the β-(2-Phenylcyclohexane)-propionic Acids

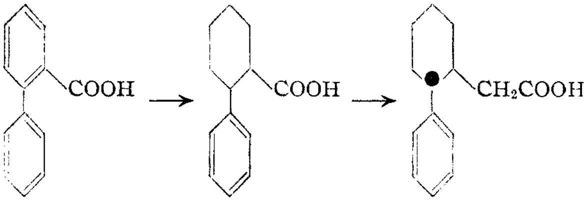
By C. David Gutsche

The preparation of the *cis* and *trans* isomers of 2-phenylcyclohexanecarboxylic acid, 2-phenylcyclohexaneacetic acid and β-(2-phenylcyclohexane)-propionic acid was undertaken because of the relation of these acids to our studies of various tricyclic ketones. The *cis* and *trans* 2-phenylcyclohexaneacetic acids have been previously prepared and their configurations unequivocally established. Cook and his co-workers[1] who first synthesized the isomers postulated the configurations from physical data.[2] Their assignment of configuration was later substantiated by the very elegant work of Linstead and his co-workers[3,4] in which the proof depended upon conclusive chemical relationships. It is this pair of acids, IIIa and IIIb,[5] that has served as a reference point in the present investigation, for through the application of known methods of chain elongation and degradation, the 2-phenylcyclohexanecarboxylic acids, Va and Vb, and the β-(2-phenylcyclohexane)-propionic acids, VIa and VIb, have been related to IIIa and IIIb and their stereochemical configurations have thereby been established.

The *cis*- and *trans*-2-phenylcyclohexaneacetic acids, the reference compounds, were synthesized by methods already described in the literature. 2-Phenyl-Δ^1-cyclohexeneacetic acid, II, prepared from 2-phenylcyclohexanone, I, according to a somewhat modified method of Cook and co-workers,[1] was catalytically hydrogenated to *cis*-2-phenylcyclohexaneacetic acid, IIIa, in 52.5% over-all yield from I. 2-Phenylcyclohexanecarboxylic acid, V, prepared by the sodium and amyl alcohol reduction of 2-phenylbenzoic acid, IV, was converted by a modification of a previously described method[6] to *trans*-2-phenylcyclohexaneacetic acid, IIIb, in 70% yield from II.



I II IIIa



IV V IIIb

The 2-Phenylcyclohexanecarboxylic Acids (V).—One of the isomers of this pair has been synthesized previously by a number of methods. Kipping and Perkin[7] first prepared 2-phenylcyclohexanecarboxylic acid, V, by the sodium ethoxide catalyzed condensation of diethyl malonate with 1-phenyl-1,5-dibromopentane followed by hydrolysis and decarboxylation. Several workers[6,8,9,10] have obtained V by the sodium and amyl alcohol reduction of 2-phenylbenzoic acid, IV. Cook and Hewett[10] and Blumenfeld[11] have employed Diels–Alder reactions between phenylbutadiene and acrolein or ethyl acrylate in the synthesis of V. All of these methods yielded the same acid melting at 107–108°,[12] and the conversion of V to IIIb suggested a *trans* configuration for this isomer. The possibility of an inversion during the chain elongation, however, could not be overlooked, for Wallis

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(1) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(2) Cook, Hewett and Robinson, *ibid.*, 168 (1939).

(3) Linstead, Whetstone and Levine, This Journal, **64**, 2014 (1942).

(4) Linstead, Davis and Whetstone, *ibid.*, **64**, 2009 (1942).

(5) The representation of configuration is that employed by Linstead [*Chemistry & Industry*, **56**, 510 (1937)] in which the positions of the hydrogen atoms are shown in the formulas by black dots, a dot indicating that the hydrogen is above the plane of the molecule.

(6) Gutsche and Johnson, This Journal, **68**, 2239 (1946).

(7) Kipping and Perkin, *J. Chem. Soc.*, 304 (1890).

(8) Ranedo and León, *Anal. soc. españ. fis. quím.*, **23**, 113 (1925) [*Chem. Zentr.*, **96**, I, 2557 (1925)].

(9) Fujise, *Ber.*, **71B**, 2461 (1938).

(10) Cook and Hewitt, *J. Chem. Soc.*, 62 (1936).

(11) Blumenfeld, *Ber.*, **74B**, 524 (1941).

(12) This is the melting point of the purest sample obtained in this Laboratory and is slightly different from those previously recorded; 103–105°,[8] 104–105°,[7] 105–106°,[9] 105–107°,[10] 110°.[11]