D,L-Rhamnitol.—A solution of 0.50 g. of D-rhamnitol and 0.50 g. of L-rhamnitol in 5 cc. of hot alcohol upon cooling deposited 0.9 g. of prisms of much the same appearance as those of its components. The substance may be recrystallized from 4 parts of alcohol the same as the D- or L-forms; it melts at 112–113° and exhibits no rotation in aqueous solution. Valentin[7] reported m. p. 117° and describes the substance as crystallizing from aqueous solution in the form of anhydrous microscopic needles.

Proof that it is a true racemate was obtained through optical measurements (see Table I). The D,L-rhamnitol shows indices of refraction which are different from those of its components; it also differs from the components in that its optic sign is positive and the axial angle 2V is 85°.

Summary

The very accessible methyl α-D-mannopyranoside, which can be produced from vegetable ivory, methyl alcohol and sulfuric acid in over 40% yield, proves to be an excellent source for the preparation of D-rhamnose, the enantiomorph of the naturally occurring L-rhamnose. The intermediates are methyl 2,3,4-tribenzoyl-6-tosyl-α-D-mannopyranoside, methyl 2,3,4-tribenzoyl-6-desoxy-6-iodo-α-D-mannopyranoside, methyl 2,3,4-tribenzoyl-α-D-rhamnopyranoside and methyl α-D-rhamnopyranoside, the last of which is hydrolyzed by acid to D-rhamnose. The over-all yield is about 28%. The reactions conclusively correlate the α-D-forms of methyl mannopyranoside and methyl rhamnopyranoside and thereby verify the previously inferred correlation of these glycosides through rotatory relations. Methyl 2,3,4-tribenzoyl-6-tosyl-α-D-mannopyranoside is readily converted to methyl 3,6-anhydro-α-D-mannopyranoside. The crystallization of several D,L-substances in the rhamnose series is described, and all of them prove to be true racemates. The use of a moderate excess of diethylamine as acceptor for hydriodic acid proves advantageous in the reduction of methyl tribenzoyl-6-desoxy-6-iodo-α-D-mannopyranoside to methyl tribenzoyl-α-D-rhamnopyranoside by hydrogen and Raney nickel.

BETHESDA, MARYLAND RECEIVED DECEMBER 26, 1945

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(7) Valentin, *Collection Czechoslov. Chem. Commun.*, **2**, 691 (1930).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Studies on the Willgerodt Reaction. II. The Mechanism of the Reaction

BY JOHN A. KING AND FREEMAN H. MCMILLAN

The first paper of this series[1,2] showed that the scope of the Willgerodt reaction was considerably broader than had previously been supposed. The present paper indicates the probable course of the reaction and offers a mechanism which satisfactorily explains all experimental data so far obtained.

In 1888 Willgerodt[3] made three significant observations relevant to the mechanism of this reaction: aldehydes are converted to the corresponding acids and amides under the conditions of the reaction; the ketone is not reduced to an alkylbenzene as an intermediate at any stage of the reaction because the latter are unchanged under the conditions of the reaction; and, because amides are almost unchanged under the conditions of the reaction, they are formed either concurrently with or, more probably, from the acids. In his later papers Willgerodt[4] found that the yield of amide decreased inversely with the chain length of the alkyl group of the ketone; this was confirmed, much later, by Bachmann and Carmack[5] and by Cavalieri and co-workers.[2] He[4] also observed that when too much sulfur was used in the reaction the ketones underwent cleavage and when too little sulfur was used alkylbenzenes and diarylthiophenes often constituted the major reaction products. He further found that sodium polysulfide could be used to convert acetophenone to phenylacetic acid. Kindler[6] was the first to use anhydrous amines and free sulfur in the reaction and obtained as products the thioamides analogous to the carboxylic amides that were formed from the same carbonyl compounds and ammonium polysulfide.

Before attempting to discover the course of the reaction it was essential to determine whether the reaction always proceeded without any rearrangement in the alkyl group. This was assumed by Willgerodt,[4] while Fieser and Kilmer[7] implied that they doubted if isovalerophenone yielded α-methyl-γ-phenylbutyramide and Bachmann and Carmack and Hartmann and co-workers[8] were non-committal. Willgerodt's assumption was shown to be correct. When the reaction was carried out on isobutyrophenone and isovalerophenone, under the same conditions as were used by Willgerodt and Merk, the products were, respectively, the α-methyl amides of β-phenylpropionic and γ-phenylbutyric acids, identified by mixed melting point determinations with authentic samples of the amides.

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(1) King and McMillan, THIS JOURNAL, **68**, 525 (1946).

(2) This is also confirmed by the work of Cavalieri, Pattison and Carmack, THIS JOURNAL, **67**, 1783 (1945), who applied the reaction to purely aliphatic and to alicyclic-aliphatic ketones.

(3) Willgerodt, *Ber.*, **21**, 534 (1888).

(4) (a) Willgerodt, *J. prakt. Chem.*, [2] **80**, 183 (1909); (b) Willgerodt and Merk, *ibid.*, [2] **80**, 192 (1909); (c) Willgerodt and Hambrecht, *ibid.*, [2] **81**, 74 (1910); (d) Willgerodt and Scholtz, *ibid.*, [2] **81**, 382 (1910).

(5) Bachmann and Carmack, THIS JOURNAL, **63**, 2494 (1941).

(6) Kindler, *Ann.*, **431**, 187 (1923).

(7) Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940).

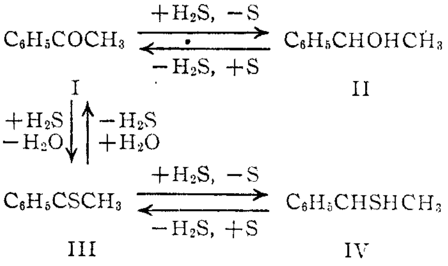
(8) Hartmann, Miescher, Kaegi and Bosshard, Canadian Patent 414,941.

Of the mechanisms already proposed for the reaction, Willgerodt's[3] is little more than a statement of the products obtained, while Kindler's mechanisms,[6,9] which employ an α,β or α,γ shift of an aryl group, are inapplicable to higher homologous ketones; for example, by Kindler's mechanism *n*-butyrophenone would yield α- or β-phenylbutyramide whereas the product obtained is γ-phenylbutyramide.

The formation of acids and amides with nonrearranged carbon skeletons excludes the use of Whitmore's mechanism of intramolecular rearrangements or of any pinacol-type rearrangement as the basis of a mechanism for the Willgerodt reaction. It seemed possible to us that no actual "rearrangement" occurs, but that instead the reaction proceeds by a progression of some group along the carbon chain. This hypothesis was tested by applying the reaction to pivalophenone, which contains in the side-chain a quaternary carbon atom past which no functional group can go. Pivalophenone gave no trace of amide; the product obtained, in good yield, was neopentylbenzene. This negative evidence is interpreted as indicating that the normal Willgerodt reaction probably does proceed *via* a progression along the side-chain.

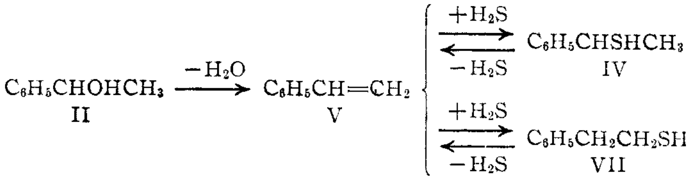
One now has the following information upon which to construct a reaction mechanism: the reaction proceeds with ketones, alcohols, olefins, acetylenes[10] and aldehydes; the reaction occurs without rearrangement; an aralkyl hydrocarbon is not an intermediate in the reaction; the reaction probably proceeds by a progression of a group along the chain; the progressional group is univalent because it can pass a tertiary carbon atom (*e. g.*, as in isobutyrophenone or isovalerophenone); the yield of amide decreases in parallel with the increasing length of the side-chain through which the group progresses; amides are formed either from or concurrently with acids; the bases which have been used are ammonia, primary and secondary amines; side reactions are complete reduction to aralkyl hydrocarbons, rupture of the side-chain to give aryl acids, and formation of thiophene derivatives. This information must be supplemented by the answer to the question: what is the univalent group that progresses along the side-chain?

The answer was sought in a consideration of the reagent used. Ammonium sulfide is a fairly common reducing agent; as a pertinent example, Baumann and Fromm[11] found that at room temperature alcoholic ammonium sulfide converted acetophenone to bis-(1-phenylethyl)-disulfide among other things. There are numerous instances of the use of sulfur as an oxidizing agent. Since ammonium polysulfide is in reality both an oxidizing and a reducing agent, we wish to suggest that the following equilibria exist, at least to a certain extent, in the Willgerodt reaction mixture. These equilibria will be shifted in whichever direction any of the products can be removed from effective participation in the equilibria, even though such removal may be several steps away from any of the substances I–IV. It is quite possible that the thiophenes formed as byproducts in the reaction may arise from thioacetophenone produced in this manner, since the formation of 2,4- and 2,5-diphenylthiophenes from thioacetophenone at elevated temperatures is well-known.[12]



$$\begin{tikzcd}
\underset{\mathrm{I}}{C_6H_5COCH_3} \arrow[r, shift left, "{+H_2S,\ -S}"] \arrow[d, shift right, "{+H_2S \atop -H_2O}"'] & \underset{\mathrm{II}}{C_6H_5CHOHCH_3} \arrow[l, shift left, "{-H_2S,\ +S}"] \\
\underset{\mathrm{III}}{C_6H_5CSCH_3} \arrow[r, shift left, "{+H_2S,\ -S}"] \arrow[u, shift right, "{-H_2S \atop +H_2O}"'] & \underset{\mathrm{IV}}{C_6H_5CHSHCH_3} \arrow[l, shift left, "{-H_2S,\ +S}"]
\end{tikzcd}$$

At the moderately high temperatures employed in the reaction (150–225°) we think it probable that the following equilibria also exist. Although step II to V is plausible enough, its reversal, the non-catalytic hydration of V to II, or occurrence of the equilibrium $V + H_2O \rightleftarrows C_6H_5CH_2CH_2OH$ (VI) seemed improbable. If II → V → VI were involved in the Willgerodt reaction, VI should yield phenylacetamide just as did styrene, phenylmethylcarbinol and acetophenone. When VI was heated with ammonium polysulfide under the same conditions as I, II and V, no trace of phenylacetamide was formed; instead, VI was recovered unchanged and identified by means of its α-naphthylurethan. Therefore, V → VI is not an intermediate stage in the reaction.



$$\begin{tikzcd}
 & & \underset{\mathrm{IV}}{C_6H_5CHSHCH_3} \arrow[dl, shift left, "-H_2S"] \\
\underset{\mathrm{II}}{C_6H_5CHOHCH_3} \arrow[r, "-H_2O"] & \underset{\mathrm{V}}{C_6H_5CH{=}CH_2} \arrow[ur, shift left, "+H_2S"] \arrow[dr, shift left, "+H_2S"] & \\
 & & \underset{\mathrm{VII}}{C_6H_5CH_2CH_2SH} \arrow[ul, shift left, "-H_2S"]
\end{tikzcd}$$

The sequence IV ⇄ V ⇄ VII however is highly probable. Jones and Reid[13] and Ipatieff and Friedman[14] have studied the addition of hydrogen

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(9) Kindler and Li, *Ber.*, **74**, 321 (1941).

(10) It seemed to us highly probable that, in accordance with the reaction mechanism developed in this paper, acetylenes would undergo the Willgerodt reaction normally. We contemplated studying them in the reaction but were deterred by the fact that, from a practical point of view, the ultimate amides or acids can usually be made more easily than the acetylenes which would be used as starting materials in the Willgerodt reaction. Carmack and DeTar, THIS JOURNAL, **68**, in press (1946), have employed acetylenes in the reaction, finding that they behave as was expected.

(11) Baumann and Fromm, *Ber.*, **28**, 907 (1895).

(12) (a) Bogert and Herrera, THIS JOURNAL, **45**, 238 (1923); (b) Campaigne, *ibid.*, **66**, 684 (1944).

(13) Jones and Reid, *ibid.*, **60**, 2452 (1938).

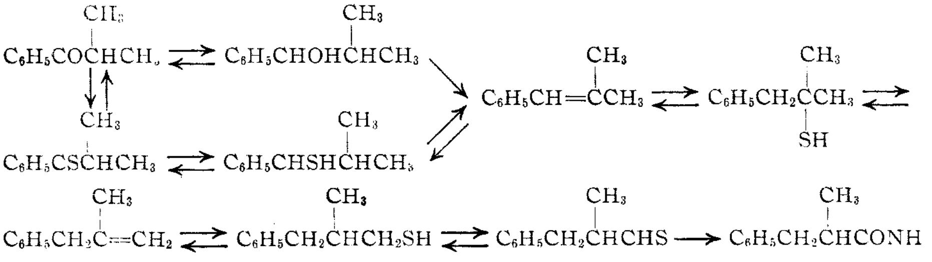
(14) Ipatieff and Friedman, *ibid.*, **61**, 71 (1939). *Cf.* references given by these authors for more examples of hydrogen sulfide addition to olefins.

sulfide to olefins. An excess of olefin favored sulfide formation and an excess of hydrogen sulfide favored mercaptan formation; whereas hydrogen sulfide added in accordance with Markownikoff's rule, various studies[15] have shown that addition of unsymmetrical reagents to a carbon–carbon double bond is rarely if ever completely unidirectional, although it may often be 95+% or even 99+% in one way. In order to determine if IV → V → VII or II → V → VII could be involved in the Willgerodt reaction VII was treated with ammonium polysulfide under the same conditions as had been used for I, II, V and VI; there was obtained a 95% yield of phenylacetamide. Thus, even though the addition of hydrogen sulfide to V might lie far in favor of IV, whatever VII was formed would participate in the equilibrium VII ⇄ VIII and VIII would be removed

$$\underset{\text{VII}}{C_6H_5CH_2CH_2SH} \underset{-S,\ +H_2S}{\overset{+S,\ -H_2S}{\rightleftarrows}} \underset{\text{VIII}}{C_6H_5CH_2CHS} \xrightarrow{+S} \underset{\text{IX}}{C_6H_5CH_2CSSH}$$

from the equilibrium mixture by oxidation to IX (or hydrolysis to CH_2CHO in aqueous media, and then oxidation). In the essentially anhydrous methods IX would give the thioamide $C_6H_5CH_2CSNR_2$ that is obtained, whereas in the aqueous methods the (mono- or) dithioacid would very rapidly be hydrolyzed to phenylacetic acid which would give the normal amide.

Such a course of reaction is equally applicable to any ketone, alcohol or olefin in which no quaternary carbon atom blocks the progression of the sulfhydryl group along the chain. For example, the stages involved in the conversion of isobutyrophenone to α-methyl-β-phenylpropionamide would be



$$C_6H_5CO\overset{CH_3}{CH}CH_3 \rightleftarrows C_6H_5CHOH\overset{CH_3}{CH}CH_3 \searrow C_6H_5CH{=}\overset{CH_3}{C}CH_3 \rightleftarrows C_6H_5CH_2\underset{SH}{\overset{CH_3}{C}}CH_3 \rightleftarrows$$
$$\downarrow\uparrow$$
$$C_6H_5CS\overset{CH_3}{CH}CH_3 \rightleftarrows C_6H_5CHSH\overset{CH_3}{CH}CH_3 \nearrow$$
$$C_6H_5CH_2\overset{CH_3}{C}{=}CH_2 \rightleftarrows C_6H_5CH_2\overset{CH_3}{CH}CH_2SH \rightleftarrows C_6H_5CH_2\overset{CH_3}{CH}CHS \longrightarrow C_6H_5CH_2\overset{CH_3}{CH}CONH$$

When the side-chain is a straight chain the various secondary thiols will be in equilibrium with the corresponding thioketones.

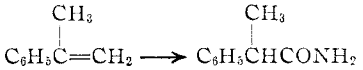
This mechanism explains very nicely why the yield of amide decreases with increasing length of the side-chain. Addition of any of the intermediate thiols to any of the intermediate olefins would remove both the addendum and the addenda from the equilibria by sulfide formation. Furthermore, the longer the chain, the greater is the opportunity for complete reduction to a saturated hydrocarbon, although generally this is not a serious side-reaction unless the temperature used is too low to cause dehydration or dehydrosulfidation to an appreciable extent, or there is a deficiency of sulfur for oxidation of the terminal mercaptan group to a thioaldehyde.

The hypothesis that an olefin is an intermediate in the reaction also serves to explain the occasional formation of cleavage products. In the oxidative cleavage of olefins it is generally accepted that a 1,2-glycol is an intermediate; and that this glycol undergoes 1,4-dehydrogenation to form a 1,4-diradical which then, in accordance with Criegee's[16] hypothesis of glycol cleavage, undergoes 2,3-scission to two smaller molecules. By analogy, sulfur as the oxidizing agent would give either a 1,2-glycol or a 1,2-dithiol (under anhydrous conditions) which could follow the same cleavage course. This is in agreement with Willgerodt's[4b] observation that too much sulfur (*i. e.*, a better opportunity for oxidation and dehydrogenation) led to extensive cleavage of the ketones.

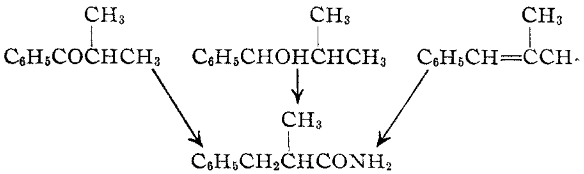
As further tests of our mechanism we have applied the reaction to allylbenzene and propenylbenzene, both of which gave β-phenylpropionamide in approximately the same yield. 2-

$$C_6H_5CH_2CH{=}CH_2 \text{ or } C_6H_5CH{=}CHCH_3 \longrightarrow C_6H_5CH_2CH_2CONH_2$$

Phenylpropene gave α-phenylpropionamide, but the yield was poor. It is probable that the low yield can be ascribed to the very great tendency toward formation of 2-phenylpropanethiol-2 instead of 2-phenylpropanethiol-1, thus allowing considerable opportunity for sulfide formation and complete reduction. As the final test of the above-proposed mechanism, it was found that both phenylisopropylcarbinol and 1-phenyl-2-methylpropene-1 yielded α-methyl-β-phenylpropionamide, the same as isobutyrophenone was found to do.



$$C_6H_5\overset{CH_3}{C}{=}CH_2 \longrightarrow C_6H_5\overset{CH_3}{CH}CONH_2$$



$$C_6H_5CO\overset{CH_3}{CH}CH_3 \quad C_6H_5CHOH\overset{CH_3}{CH}CH_3 \quad C_6H_5CH{=}\overset{CH_3}{C}CH_3 \longrightarrow C_6H_5CH_2\overset{CH_3}{CH}CONH_2$$

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(15) (a) Kharasch and Potts, *J. Org. Chem.*, **2**, 195 (1937), and numerous papers by Kharasch and co-workers on "The Peroxide Effect" in THIS JOURNAL, 1933 to date. *Cf.* also Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940). (b) Kozacik and Reid, THIS JOURNAL, **60**, 2436 (1938).

(16) Criegee, *Ber.*, **68**, 665 (1935).

Further work on the Willgerodt reaction has been and is being carried out. This will be reported at a future date.

Experimental Part[17,18]

Isobutyrophenone and Ammonium Polysulfide.—Three grams of isobutyrophenone[19] and fifteen grams of yellow ammonium sulfide[1,4b] were heated five and one-half hours at 195–200° in a pressure tube.[1] The reaction mixture was extracted with ether, the solvent was removed from the extract and the residue was extracted with boiling water. The aqueous extract was concentrated to a small volume and the resultant solid (*ca.* 100 mg., 3% yield) was recrystallized twice from water to give colorless crystals, m. p. 106–107°. When these were mixed with an authentic sample[20a] of α-methyl-β-phenylpropionamide the mixture melted at 107–107.5°. When the material was mixed with an authentic sample[20b] of β-methyl-β-phenylpropionamide the mixture melted at 87–100°. A mixture of the two authentic samples of α-methyl-β-phenylpropionamide and β-methyl-β-phenylpropionamide (β-phenylbutyramide) melted at 87–92°.

Isovalerophenone and Ammonium Polysulfide.—According to the procedure of Willgerodt and Merk,[4b] 3 g. of isovalerophenone[19] and fifteen grams of ammonium polysulfide were heated twenty-four hours at 195–200°. The reaction mixture was worked up as described for isobutyrophenone to yield *ca.* 200 mg. (6% yield) of solid which melted at 119–120° after two recrystallizations from water. When this was mixed with an authentic sample[20c,21] of α-methyl-γ-phenylbutyramide the mixture melted at 119–120°.

Pivalophenone and Ammonium Polysulfide.—Pivalophenone[22] (3 cc.) and ammonium polysulfide (15 g.) were heated thirty hours at 205°. The reaction mixture was extracted with ether, the extract was washed five times with water and was then dried. After removal of the solvent the residue was distilled at 85–90° (23 mm.); there was 2.0 cc. of distillate. This distillate would not give a 2,4-dinitrophenylhydrazone, although pivalophenone readily gave the derivative reported by Ford and coworkers. Neither would it give an α-naphthylurethan, although phenyl-*t*-butylcarbinol[23] easily gave this derivative. The material was found to be insoluble in cold conc. sulfuric acid and was thereby recognized as having a saturated hydrocarbon side-chain. It was nitrated, reduced and acetylated by the method of Ipatieff and Schmerling[24] to give 2,4-bis-(acetamino)-neopentylbenzene, m. p. 240–241°, undepressed when mixed with an authentic sample.[25] If pivalophenone and ammonium polysulfide were heated any less than twenty-four hours the extract, after removal of the ether, had a vile odor and distilled over a wide range with much decomposition. Presumably it consisted of 1-phenyl-2,2-dimethylpropyl mercaptan, -sulfide, -disulfide and -polysulfides which were intermediate in the complete reduction to neopentylbenzene.

2-Phenylethanol and Ammonium Polysulfide.—2-Phenylethanol[26] (2 cc.) and ammonium polysulfide (10 g.) were heated four hours at 205 ± 5°. No solid was obtained. Ether extraction of the mixture, after washing and drying of the extract and removal of the solvent, left 2 cc. of liquid which readily formed an α-naphthylurethan that melted, after recrystallization from chloroform–Skelly B, at 116° alone or when mixed with an authentic sample of the α-naphthylurethan of 2-phenylethanol.

2-Phenylethanethiol and Ammonium Polysulfide.—2-phenylethanethiol[27] (1.00 g.) and ammonium polysulfide (5 g.) were heated four hours at 205 ± 5°. The contents of the tube were evaporated to dryness and the residue was leached with hot ethanol. From the alcoholic extract there was obtained 0.93 g. (95% yield) of crystalline solid which melted, after one recrystallization from water, at 153–154°, undepressed when mixed with an authentic sample of phenylacetamide.

Allylbenzene and Ammonium Polysulfide.—Allylbenzene[28] (3 cc.) and ammonium polysulfide (15 g.) were heated five hours at 205 ± 5°. The crystalline solid (*ca.* 1.5 g., crude) was filtered from the reaction mixture and recrystallized from water to give colorless crystals of β-phenylpropionamide, m. p. and mixed m. p. 100–101°.

Propenylbenzene and Ammonium Polysulfide.—Quantities, procedure and product were identical with that just described for allylbenzene and ammonium polysulfide, except that twice-fractionated propenylbenzene[28] was used.

2-Phenylpropene and Ammonium Polysulfide.—2-Phenylpropene[29] (3 cc.) and ammonium polysulfide (15 g.) were heated five hours at 195–200°. The reaction mixture was extracted with ether, the extract was washed and dried and the solvent was removed. Addition of Skelly B to the liquid caused the separation of a crystalline solid (*ca.* 100 mg., 3% yield), m. p. 93°. When this was mixed with an authentic sample of hydratropamide[20d] the mixture melted at 93–94°.

Phenyl-isopropylcarbinol and 1-Phenyl-2-methylpropene in the Willgerodt Reaction.—Both the carbinol and the olefin[30] were run at the same time. Three cc. of the compound and 15 g. of ammonium polysulfide were heated six hours at 200°. The reaction mixture was extracted with ether, the extract was washed three times with water and the solvent was removed to leave a yellow oil. Skelly A was added to the oil and that obtained from the olefin deposited a white crystalline precipitate (*ca.* 75 mg.) of

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(17) Melting points and boiling points are uncorrected.

(18) Inasmuch as we were more interested for the present purpose in determining whether the Willgerodt reaction went at all than in obtaining optimal yields of amides it is possible that the yields of amides reported herein may be improved by suitable variation of the reaction conditions.

(19) von Braun and Schattner, *Ber.*, **74B**, 22 (1941). The same general method was used by us for the preparation of isovalerophenone.

(20) Our authentic amide samples were prepared by the unequivocal malonic ester method. (a) $CH_2(COOC_2H_5)_2 \rightarrow C_6H_5CH_2CH(COOC_2H_5)_2 \rightarrow C_6H_5CH_2C(CH_3)(COOC_2H_5)_2 \rightarrow$ diacid $\rightarrow$ monoacid $\rightarrow$ acid chloride $\rightarrow$ amide, m. p. 108.5°. Edeleano, *Ber.*, **20**, 618 (1887), reported the m. p. as 109°. (b) $CH_2(COOC_2H_5)_2 \rightarrow C_6H_5CH(CH_3)CH(COOC_2H_5)_2 \rightarrow$ diacid $\rightarrow$ monoacid $\rightarrow$ acid chloride $\rightarrow$ amide, m. p. 106.5–107°. Kohler and Reimer, *Am. Chem. J.*, **33**, 353 (1905), reported the m. p. as 105°. (c) $CH_2(COOC_2H_5)_2 \rightarrow C_6H_5CH_2CH_2CH(COOC_2H_5)_2 \rightarrow C_6H_5CH_2CH_2C(CH_3)(COOC_2H_5)_2 \rightarrow$ diacid $\rightarrow$ monoacid $\rightarrow$ acid chloride $\rightarrow$ amide, m. p. 119–120°. Willgerodt and Merk reported the m. p. as 118°. (d) $C_6H_5CH(COOC_2H_5)_2 \rightarrow C_6H_5C(CH_3)(COOC_2H_5)_2 \rightarrow$ diacid $\rightarrow$ monoacid $\rightarrow$ acid chloride $\rightarrow$ amide, m. p. 93–94°. Janssen, *Ann.*, **250**, 136 (1889), gave the m. p. as 91–92°.

(21) The equivalence of the amide prepared by the method of ref. 20c (von Braun and Kirschbaum, *Ber.*, **47**, 262 (1914)) with the one prepared from isovalerophenone shows that von Braun and Kirschbaum erred in stating that the α-methyl-γ-phenylbutyric acid prepared by their method was not the same as that of Willgerodt and Merk.

(22) Ford, Thompson and Marvel, THIS JOURNAL, **57**, 2619 (1935); these authors reported the b. p. as 80–84° (3 mm.); our material b. p. 86–90° (5 mm.).

(23) Ramart-Lucas, *Ann. chim.*, [8] **30**, 361 (1913). The α-naphthylurethan melted at 163–164° after one recrystallization from chloroform–Skelly B. *Anal.* Calcd. for $C_{22}H_{23}NO_2$: N, 4.21. Found: N, 4.03. (Analysis by Mrs. Gladys Barnett.)

(24) (a) Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937); (b) *ibid.*, **60**, 1476 (1938).

(25) Bygden, *Ber.*, **45**, 3479 (1912).

(26) Bouveault and Blanc, *Bull. soc. chim.*, [3] **31**, 675 (1904).

(27) Prepared in 78% yield by the general procedure of Urquhart, Gates and Conner, "Organic Syntheses," **21**, 36 (1941); b. p. 104° (17 mm.). von Braun, *Ber.*, **45**, 1564 (1912) reported the b. p. as 105° (23 mm.).

(28) Tiffeneau, *Compt. rend.*, **139**, 482 (1904).

(29) Tissier and Grignard, *Compt. rend.*, **132**, 685 (1901).

(30) Conant and Blatt, THIS JOURNAL, **50**, 554 (1928). Our carbinol was dehydrated by distillation over fused potassium acid sulfate.

α-methyl-β-phenylpropionamide, m. p. 104–106°; when this was mixed with an authentic sample of the amide (m. p. 108.5°) the mixture melted at 106–108°. No solid separated from the oil obtained from the carbinol. The Skelly A was removed by distillation and the oil was extracted with boiling water. Concentration of the aqueous extract to a small volume, followed by refrigeration, yielded *ca.* 100 mg. of crystalline amide, m. p. 105–107°, undepressed when mixed with an authentic sample of α-methyl-β-phenylpropionamide.

Summary

A mechanism has been proposed for the Willgerodt reaction. This mechanism has been supported by experimental results and it has been demonstrated how all of the previously existing data on the reaction fit into this mechanism.

The reaction has been extended to a number of ketones, alcohols and olefins to which the Willgerodt reaction has not previously been applied.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 22, 1945

[CONTRIBUTION FROM THE ARMOUR LABORATORIES]

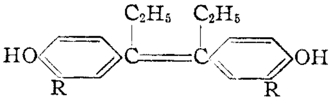
Preparation of New Derivatives of Diethylstilbestrol and Hexestrol by the Claisen Rearrangement[1]

BY EMIL KAISER AND J. J. SVARZ

The influence of various aliphatic radicals and unsaturated groups on the estrogenic activity of α,α'-substituted stilbestrol has been thoroughly investigated by Dodds, Golberg, Lawson and Robinson[2]; however, the introduction of these groups into the aromatic nuclei of diethylstilbestrol and hexestrol has not been described. Therefore we decided to prepare a new series of 3,3'-allyl, propenyl and propyl substituted synthetic estrogens by applying the Claisen rearrangement[3] to the diallyl ethers of diethylstilbestrol and hexestrol. The diallyl ethers of diethylstilbestrol and hexestrol, not previously described, were prepared by reacting diethylstilbestrol and hexestrol with allyl bromide in the presence of potassium carbonate in methyl ethyl ketone. The Claisen rearrangement of the diallyl ethers yielded 3,3'-allyldiethylstilbestrol (I) and 3,3'-allylhexestrol (II). Both compounds were benzoylated and the benzoic esters were found to be insoluble in ether. By heating the 3,3'-allyldiethylstilbestrol and 3,3'-allylhexestrol in a solution of potassium hydroxide in diethyleneglycol according to Fletcher and Tarbell,[4] a shifting of the double bonds in the side chains occurred and the corresponding propenyl derivatives were formed. The reaction did not proceed smoothly. The solution turned dark and the product was mostly resinified even when the heating was carried out in an atmosphere of nitrogen. The 3,3'-propenyldiethylstilbestrol (III) and 3,3'-propenylhexestrol (IV) were obtained in low yields. To improve the yields a small amount of concentrated sodium hydrosulfite solution was added to the reaction mixture. Although little of the sodium hydrosulfite dissolved in the diethyleneglycol, losses due to discoloration and resinification were greatly reduced and the yields improved.

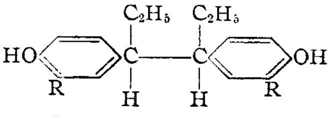
The 3,3'-propenyldiethylstilbestrol and 3,3'-propenylhexestrol have the double bonds of the side chains in a conjugated position to the double bonds of the aromatic nuclei. This configuration renders both compounds susceptible to light. Exposed to light the 3,3'-propenyldiethylstilbestrol turns yellow much faster than the 3,3'-propenylhexestrol.

The 3,3'-allylhexestrol was hydrogenated over platinum oxide and the saturated 3,3'-propylhexestrol (V) isolated and crystallized.



I, R = $CH_2CH{=}CH_2$

III, R = $CH{=}CHCH_3$



II, R = $CH_2CH{=}CH_2$

IV, R = $CH{=}CHCH_3$

V, R = $CH_2CH_2CH_3$

The estrogenic activities of the new compounds, compared with estrone as a standard, are shown in Table I.

Introduction of the propenyl groups into the aromatic nuclei of diethylstilbestrol results in the greatest loss of activity in this series. The 3,3'-propenyldiethylstilbestrol is $^1/_{1250}$ to $^1/_{2500}$ as strong in estrogenic activity as the diethylstilbestrol. Dodds, Golberg, Lawson and Robinson[2] found that the substitution of the α,α'-ethyl groups by propenyl groups causes a 150-fold drop of estrogenic activity. This loss is only about one-tenth as much as the loss of estrogenic activity caused by the substitution into the aromatic nuclei.

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(1) Paper given at the November, 1945, meeting of the Chicago Section of the American Chemical Society at the Northwestern Institute of Technology, Evanston, Illinois.

(2) (a) Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); (b) *ibid.*, **142**, 34 (1938); (c) *Proc. Roy. Soc.* (London), **127B**, 140 (1939).

(3) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 1.

(4) Fletcher and Tarbell, THIS JOURNAL, **65**, 1431 (1943).