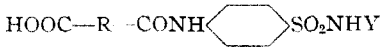
[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME]

Dicarboxylic Acid Derivatives of Sulfonamides[1]

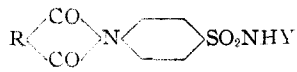
BY MAURICE L. MOORE AND CHARLES S. MILLER

In continuing our studies of the possible chemotherapeutic activity of sulfonamide compounds,[2] it was found that certain of the derivatives from dicarboxylic acids possessed interesting activity as intestinal antiseptics. We undertook to prepare a large series of these compounds, some of which have been studied as intestinal antiseptics.[3] One of these, succinylsulfathiazole,[4,5] has shown unusually marked activity for this purpose. In this paper we describe the preparation and properties of these compounds and discuss some of the results obtained from the reactions involved in their preparation.

The condensation of succinic, maleic and phthalic anhydrides with the various sulfonamides, using anhydrous alcohol or dioxane as a solvent according to the method previously described for the sulfanilamide and sulfanilhydroxamide derivatives,[2b,c] occurred in the ratio of 1:1, giving monobasic acids of the general formula I. Condensa-



I

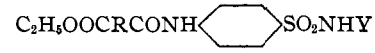


II

tion of succinic anhydride with sulfanilamide in the presence of pyridine had been found to give the anil II.[2c] Recently, Shapiro and Bergmann[6] have found that in the condensation of sulfapyridine with succinic and phthalic anhydrides temperatures below 100° give acid amides I while temperatures above 100° give the anils II. They found that with maleic anhydride the acid amide was the sole reaction product, even at 190°. However, neither Shapiro and Bergmann nor we had obtained any of the diamides III in condensations with anhydrides.

III

The oxalic and malonic acid derivatives of sulfathiazole, sulfadiazine and sulfaguanidine were made by refluxing the sulfonamide with an excess of the ethyl ester of the appropriate acid and hydrolyzing the ester amides IV thus formed with



IV

alkali to give the corresponding acid amides. The ester amides were obtained in yields above 80%, although, in most cases there was isolated a small quantity of by-product which appeared to be the diamide. Esters of higher acids, such as ethyl glutarate and sebacate, did not condense with sulfathiazole even when heated at 160–170° for two hours.

The higher acid derivatives, *i. e.*, from glutaric, adipic and sebacic acids, were made by heating the sulfonamide with the acid itself at a temperature between 150–170° for one to two hours. Succinylsulfathiazole (compound no. 8) was also prepared in this manner and the reaction studied in some detail. It appears that with an equimolar mixture of the components, or with as much as 5 or 10% excess of the acid, the reaction proceeded with the formation of the anil and about 5–7% of the diamide. Hydrolysis of the anil with 5–10% sodium hydroxide solution gave the acid amide which was removed from the diamide by solubility in cold bicarbonate solution. Similar results have been obtained by carrying out the condensation in refluxing "Carbitol."

Condensation of adipic acid with sulfapyridine, sulfathiazole and sulfaguanidine, followed by treatment with alkali, led to the isolation of the acid amides and the diamides, with a larger portion of the product being the diamides. However, with glutaric and sebacic acids, the diamides were the principal product from the condensation with sulfathiazole.

Attempts to condense *p*-succinimidobenzenesulfonyl chloride with 2-aminothiazole led to some interesting observations. With two equivalents of 2-aminothiazole, in pyridine or acetone as a sol-

(1) This paper was presented before the Division of Medicinal Chemistry of the American Chemical Society in Memphis, April, 1942.

(2) (a) Moore and Miller, THIS JOURNAL, **63**, 2781 (1941); (b) Moore, Miller and Miller, *ibid.*, **62**, 2097 (1940); (c) Miller, Rock and Moore, *ibid.*, **61**, 1198 (1939).

(3) Poth and Knotts, *Arch. Surg.*, **44**, 187 (1942).

(4) To this compound Sharp and Dohme has applied its trademark "Sulfasuxidine."

(5) (a) Poth and Knotts, *Proc. Soc. Exp. Biol. and Med.*, **48**, 129 (1941); (b) Poth and Knotts, *Arch. Surg.*, **44**, 208 (1942).

(6) Shapiro and Bergmann, *J. Org. Chem.*, **6**, 774 (1941).

vent, the acid amide was obtained in about a 1:1 ratio with an unidentified product. Similar results were obtained with 1 equivalent of 2-aminothiazole in sodium carbonate solution.

Experimental

1. **Anhydride Condensations.**—Five hundred grams (1.96 moles) of sulfathiazole was added to 5000 cc. of anhydrous alcohol and heated to refluxing with mechanical stirring. When refluxing occurred, 250 g. (2.5 moles, 25% excess) of succinic anhydride was added and the mixture refluxed for forty-five minutes. During this period, all of the materials had gone into solution and toward the end of the reaction a solid began to crystallize out, which after standing overnight was obtained in a yield of 90%. Yields equally as good were obtained by using only 5 or 10% excess of succinic anhydride. Purification was effected by recrystallizing 104 g. of the crude material from a refluxing solution of 400 cc. of alcohol and 300 cc. of water. The yield was 89 g. (77%), melting at 192–195°, with decomposition.

Dioxane was used as the solvent for the condensation of succinic anhydride with 2-sulfanilamido-5-ethyl-4-thiazolone, sulfadiazine and sulfanilylsulfathiazole.

2. **Ester Condensations.**—Twenty grams (0.078 mole) of sulfathiazole was added to 60 g. (0.375 mole) of ethyl malonate and heated under reflux at a temperature of 130–150° for two hours. After cooling the reaction mixture to room temperature, the solid product was filtered and washed thoroughly with dilute hydrochloric acid and water. A yield of 24.7 g. (85%) of the ester amide IV, compound no. 6, was obtained and after purification by recrystallizing from dilute alcohol, it melted at 193–194.5° with decomposition.

A similar yield was obtained when only two equivalents of the ethyl malonate was used under the same experimental conditions. However, in this experiment, a small quantity of material was obtained which was insoluble in dilute alcohol. On crystallization from methyl "Cellosolve" and water, this product melted at 233–236° with decomposition. A mixed melting point with acetylsulfathiazole, m. p. 256–257°, was 225–226° followed by decomposition. Reactions and analysis suggest that the product was the diamide, **malonamide-4,4′-bis-(2-benzenesulfonamidothiazole)**.

Anal. Calcd. for $C_{21}H_{18}O_6N_6S_4$: N, 14.53. Found: N, 14.00.

An 86% yield of ester amide was obtained by condensing sulfathiazole with two equivalents of ethyl oxalate under the above conditions and no diamide was isolated.

Hydrolysis of the ethyl malonylsulfathiazole to the acid amide was accomplished by heating 14 g. of the material in 150 cc. of 2.5% sodium hydroxide solution at 85–95° for one-half hour. The solution was decolorized with charcoal (Darco) and the product precipitated from the solution by neutralization with dilute hydrochloric acid. A yield of 10 g. (77%) was obtained and after several recrystallizations from dilute alcohol the malonylsulfathiazole decomposed in the range of 240–250°, without definitely melting.

3. **Acid Condensations.**—(A) Ten grams (0.0392 mole) of sulfathiazole and 4.6 g. (0.0392 mole) of succinic acid were mixed in a flask and heated in a sand-bath to a temperature of 150–160° for one hour, with occasional stirring. At the end of the hour, the reaction melt began to solidify, while stirring, as a granular solid. The material was treated with a boiling solution of 90% acetic acid and an insoluble product filtered. The yield was 0.9 g. and melted at 277–279° with decomposition after purification by dissolving in dilute ammonia and precipitating with dilute hydrochloric acid. The product was soluble in dilute ammonia and alkali but insoluble in cold sodium bicarbonate solution. This corresponded to the diamide III, **succinamido-4,4′-bis-(2-benzenesulfonamidothiazole)**.

Anal. Calcd. for $C_{22}H_{20}O_6N_6S_4$: N, 14.19. Found: N, 14.13.

The hot acetic acid filtrate from the above was allowed to cool overnight and a white crystalline solid was obtained. The yield of the product was 5.6 g. and it melted at 266–267° after recrystallization from anhydrous methyl "Cellosolve." It was soluble in dilute ammonia and alkali but insoluble in cold sodium bicarbonate solution. This corresponded to the anil II, **2-(4′-succinimidobenzenesulfonamido)-thiazole.**

Anal. Calcd. for $C_9H_{11}O_4N_3S_2$: N, 12.46. Found: N, 12.30.

A sample of the anil was converted into the acid amide, succinylsulfathiazole, by dissolving in a warm 2.5% sodium hydroxide solution and precipitating with dilute hydrochloric acid. The product was readily soluble in cold sodium bicarbonate solution with the evolution of carbon dioxide and it melted at 140° with decomposition. After several crystallizations from dilute alcohol the product melted at 185–187° with decomposition.

A sample of the diamide was dissolved in 5% sodium hydroxide solution, refluxed for a few minutes and after cooling to room temperature the solution was carefully neutralized with dilute hydrochloric acid giving sulfathiazole; m. p. 196°. A mixed sample with authentic sulfathiazole, m. p. 199–200°, melted at 199–200°.

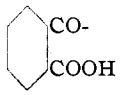
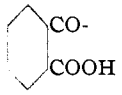
(B) Ten grams of sulfathiazole and 4.6 g. of succinic acid were heated together under the same conditions as described above. The solid obtained from the reaction mixture was dissolved in dilute ammonia, the solution decolorized with charcoal (Darco), and precipitated by the careful addition of a slight excess of dilute hydrochloric acid. A yield of 9.9 g. of an unidentified product (A) was obtained which melted at 194.5–195.5° after four recrystallizations from methyl "Cellosolve" and water. It was insoluble in cold bicarbonate solution. *Anal.* Found: N, 14.63. The identity of this compound is being investigated.

Four grams of the above compound was dissolved in 50 cc. of 5% sodium hydroxide solution and heated at about 90° for ten minutes. The acid amide, succinylsulfathiazole, melting at 129–133° with decomposition, was isolated by precipitation with dilute hydrochloric acid and after several recrystallizations from dilute alcohol melted at 185–187°.

(C) Sulfathiazole, 100 g. (0.392 mole), and 48.8 g. (0.411 mole) of succinic acid were mixed in a liter flask and heated

TABLE I

N^4-ACYL-N^1-SUBSTITUTED SULFANILAMIDES

N^4-Acyl	N^1-Substituent	Method of preparation	Yield, %	M. p., °C.[a] (uncor.)	Formula	Nitrogen analyses, %[b,c] Calcd.	Found
$HOOC(CH_2)_2CO$-	2-Pyridyl	1	81	135–140[d,e]	$C_{15}H_{13}O_5N_3S$	12.01	11.99
$HOOCCH{=}CHCO$-[f]	2-Pyridyl	1	..	193–194[d]	$C_{15}H_{13}O_5N_3S$	12.08	12.11
$HOOC(CH_2)_4CO$-[g]	2-Pyridyl	3E	11	184–185°	$C_{17}H_{19}O_5N_3S$	11.12	11.07
C_2H_5OOCCO-	2-Thiazolyl	2	88	233–234	$C_{13}H_{13}O_5N_3S_2$	11.83	11.95
$HOOCCO$-[a,h]	2-Thiazolyl	2	82	207–208	$C_{11}H_9O_5N_3S_2$	12.84	12.70
$C_2H_5OOCCH_2CO$-	2-Thiazolyl	2	85	193–194.5	$C_{14}H_{15}O_5N_3S_2$	11.38	11.31
$HOOCCH_2CO$-	2-Thiazolyl	2	76	240–250's	$C_{12}H_{11}O_5N_3S_2$	12.31	12.14
$HOOC(CH_2)_2CO$-	2-Thiazolyl	1, 3A, 3B, 3C, 3D	90	192–195[i]	$C_{13}H_{13}O_5N_3S_2$	11.83[j]	11.66
$HOOCCH{=}CHCO$-[k]	2-Thiazolyl	1	..	215–216	$C_{13}H_{11}O_5N_3S_2$	11.90	11.79
$HOOC(CH_2)_3CO$-	2-Thiazolyl	3E	56	196–197	$C_{14}H_{15}O_5N_3S_2$	11.38	11.32
$HOOC(CH_2)_4CO$-[f]	2-Thiazolyl	3E	47	196–197°	$C_{15}H_{17}O_5N_3S_2$	10.96	10.82
$HOOC(CH_2)_8CO$-	2-Thiazolyl	3F	..	171–172°	$C_{19}H_{25}O_5N_3S_2$	9.56	9.43
	2-Thiazolyl	1	72	260's[u]	$C_{13}H_{13}O_5N_3S_2$	10.42	10.43
$HOOC(CH_2)_2CO$-[l]	2-(5-ethyl-4-	1	82	161–162	$C_{15}H_{17}O_6N_3S_2$	10.52	10.45
$HOOCCH{=}CHCO$-	thiazolonyl)	1	..	179–181	$C_{15}H_{15}O_6N_3S_2$	10.58	10.78
$HOOC(CH_2)_2CO$-	2-(5,5-diethyl-4-thiazolonyl)	1	82	208–209	$C_{17}H_{21}O_6N_3S_2$	9.83	9.70
$C_2H_5OOCCH_2CO$-	Guanyl	2	80	225–226	$C_{12}H_{16}O_5N_4S$	17.07	17.33
$HOOCCH_2CO$-[f]	Guanyl	2	53	172–175[m]	$C_{10}H_{12}O_5N_4S$	18.66	18.71
$HOOC(CH_2)_2CO$-	Guanyl	1	60	214–215	$C_{11}H_{14}O_5N_4S$	17.83	17.89
$HOOCCH{=}CHCO$-	Guanyl	1	78	201–202	$C_{11}H_{12}O_5N_4S$	17.94[n]	18.00
$HOOC(CH_2)_4CO$-	Guanyl	3E	18	132–133°	$C_{13}H_{18}O_5N_4S$	16.37	16.26
	Guanyl	1	78	266–267°	$C_{15}H_{14}O_5N_4S$	15.47	15.44
C_2H_5OOCCO-[p]	2-Pyrimidyl	2	61	230–235	$C_{14}H_{16}O_5N_4S$	15.99	15.87
$HOOCCO$-	2-Pyrimidyl	2	96	250's[o]	$C_{12}H_{10}O_5N_4S$	17.39	17.70
$C_2H_5OOCCH_2CO$-[p]	2-Pyrimidyl	2	84	198–199°	$C_{15}H_{16}O_5N_4S$	15.38	15.43
$HOOCCH_2CO$-	2-Pyrimidyl	2	87	215–216°	$C_{13}H_{12}O_5N_4S$	16.66	16.91
$HOOC(CH_2)_2CO$-[q,l]	2-Pyrimidyl	1	91	212–213	$C_{14}H_{14}O_5N_4S$	15.99	16.14
$HOOC(CH_2)_4CO$-	2-Pyrimidyl	3C	..	188	$C_{16}H_{18}O_5N_4S$	14.81	14.95
$HOOC(CH_2)_2CO$-[f]	2-(4-Methyl-pyrimidyl)	1	49	201–202[q]	$C_{15}H_{16}O_5N_4S$	15.38	15.27
$HOOC(CH_2)_2CO$-[r,s]	4-Sulfamylphenyl	1	95	234	$C_{16}H_{17}O_7N_3S_2$	9.83	9.85
$HOOC(CH_2)_2CO$-[r,l,t]	4-(2-Thiazolylsulf-amyl)-phenyl	1	81	237	$C_{19}H_{18}O_7N_4S_2$	10.98	10.99

[a] Most of these compounds actually decomposed with effervescence instead of melting. In some cases these decomposition ranges were difficult to recheck. [b] The analyses were carried out in these laboratories by Mr. John R. Taylor. [c] All samples were dried in the Abderhalden dryer for at least one hour before analyzing. [d] Shapiro and Bergmann [*J. Org. Chem.*, **6**, 774 (1941)] reported a melting point of 145° for the succinyl derivative and 208° for the maleyl derivative without mentioning their decomposition. [e] A sample of this compound decomposed at 191–194° after standing for seven months. *Anal.* Found: N, 11.94. [f] Recrystallized from water. [g] Purified by dissolving in dilute ammonia and precipitating with dilute hydrochloric acid. [h] Hygroscopic; takes up water during weighing. [i] The first samples of this compound decomposed at 184–186°. *Anal.* Found: N, 11.60. After standing for six months the same samples decomposed at 192–195°. All subsequent samples prepared by the anhydride condensation have decomposed at the higher range. [j] *Anal.* before drying. Calcd. for $C_{13}H_{13}O_5N_3S_2 \cdot H_2O$: N, 11.26. Found: N, 11.21. [k] This compound is unstable in solution and is subject to hydrolysis. [l] The anhydride condensation was carried out in dioxane as the solvent. [m] A sample of this compound was heated at the melting point until no further decomposition occurred. After recrystallizing from water it melted at 260–261°. Mixed with an authentic sample of N^4-acetylsulfanilylguanidine, m. p. 266–267°, it melted at 260–262°. [n] *Anal.* before drying. Calcd. for $C_{11}H_{12}O_5N_4S \cdot H_2O$: N, 16.97. Found: N, 17.00. [o] Melted to a clear liquid. [p] Recrystallized from methyl "Cellosolve" and water. [q] Solidified after melting at this temperature and remelted at 270°. [r] We are indebted to Dr. T. M. Immediata for the preparation of these compounds. [s] Recrystallized from acetone and water. [t] Recrystallized from dioxane and water. [u] Charred instead of melting.

in an oil-bath to approximately 165° for one hour with stirring. At the end of this time, the reaction melt had begun to solidify and the flame was removed from the oil-bath. With the flask still in the oil-bath, 380 cc. of 10% sodium hydroxide solution was cautiously added and after stirring for about fifteen minutes all of the solid had dissolved. After cooling to room temperature, the alkali solution was poured into a mixture of 88 cc. of concentrated hydrochloric acid and 960 cc. of water giving 130 g. of crude product (melting at 129–135° with decomposition), which was removed by filtration and purified by dissolving in a solution of 1000 cc. of ethanol and 200 cc. of water, decolorizing with charcoal (16 g. of Norite) and filtering with the aid of 16 g. of Filter-cel. Crystallization was completed by the addition of 504 cc. of water and 40 cc. of concentrated hydrochloric acid. The yield of succinylsulfathiazole was 87.5 g., which after further crystallization from dilute alcohol melted at 138–140°.

The diamide formed was removed by the Norite and Filter-cel and was isolated by treating with dilute alkali, filtering and precipitating with dilute hydrochloric acid. A yield of 6–9 g. was obtained.

(D) One hundred grams of sulfathiazole and 48.8 g. of succinic acid were heated together in 100 cc. of diethyl "Carbitol" under the same conditions as described in (C) above, for two hours. During the heating all of the materials went into solution and at the end of one and one-half hours a solid began to precipitate. After standing overnight, the product was filtered, dissolved in 400 cc. of 10% sodium hydroxide and precipitated with dilute hydrochloric acid. A yield of 81.9 g. (59%) of succinylsulfathiazole was obtained after recrystallization from dilute alcohol. Eight grams of crude diamide was recovered from the Norite and Filter-cel.

(E) Ten grams (0.0467 mole) of sulfaguanidine was mixed with 6.7 g. (0.0467 mole) of adipic acid and heated at 140–150° for one hour. After standing overnight, the solid was treated with 60 cc. of 10% sodium carbonate solution and the insoluble product filtered. A yield of 8 g. was obtained, melting at 234–240° with decomposition. After having been washed with dilute ammonia, hydrochloric acid and water and recrystallized from methyl "Cellosolve," the product melted at 268–269° with decomposition. It corresponded to the diamide, **adipamido-4,4'-bis-(benzenesulfonylguanidine)**.

Anal. Calcd. for $C_{20}H_{26}O_6N_8S_2$: N, 20.82. Found: N, 20.51.

The carbonate soluble filtrate was neutralized with dilute hydrochloric acid and a yield of 2.8 g. of adipoylsulfaguanidine was obtained, melting at 132–133° after recrystallization from dilute alcohol.

Similar results were obtained by the condensation of adipic acid with sulfapyridine and sulfathiazole.

(F) Ten grams (0.0392 mole) of sulfathiazole was mixed with 7.9 g. (0.0392 mole) of sebacic acid and heated to 150–170° for one and one-half hours. The cooled solid reaction mixture was treated with 200 cc. of 5% sodium hydroxide solution, decolorized with charcoal (Darco) and precipitated with dilute hydrochloric acid. The crude product (14 g.) was extracted thoroughly with saturated sodium bicarbonate solution, leaving 7.5 g. of insoluble material which was thoroughly washed with dilute hydrochloric acid and water and crystallized from dilute methyl "Cellosolve" containing a small amount of sodium bicarbonate. Purification by further crystallization from dilute methyl "Cellosolve" gave the diamide, **sebacamido-4,4'-bis-(2-benzenesulfonamidothiazole)**, melting at 245–246°.

Anal. Calcd. for $C_{28}H_{32}O_6N_6S_4$: N, 12.42. Found: N, 12.31.

Acidification of the sodium bicarbonate solution gave unreacted sebacic acid, m. p. 133°.

Glutaramido-4,4'-bis-(2-benzenesulfonamidothiazole), melting at 251–254° with decomposition after crystallization from dilute methyl "Cellosolve," was obtained in the same manner from glutaric acid and sulfathiazole.

Anal. Calcd. for $C_{23}H_{22}O_6N_6S_4$: N, 13.84. Found: N, 13.56.

Succinimidobenzenesulfonyl chloride was prepared by the method reported by Adams, Long and Jeanes.[7] However, the compound was purified by two recrystallizations from acetone and water, melting at 189–195° with decomposition.

Anal. Calcd. for $C_{10}H_8O_4NSCl$: N, 5.12. Found: N, 5.10.

Condensation of Succinimidobenzenesulfonyl Chloride with 2-Aminothiazole.—Twenty grams (0.2 mole) of 2-aminothiazole was dissolved in 75 cc. of anhydrous pyridine and 27.4 g. (0.1 mole) of succinimidobenzenesulfonyl chloride was added slowly with stirring. After the addition, the solution was heated on the steam-bath for one-half hour and the pyridine was then removed by distillation under reduced pressure. The residue was triturated with 50 cc. of cold water and the brown insoluble solid (4 g.) was filtered. After purification by several recrystallizations from dioxane and water the solid melted at 250.5–251.5° with decomposition. It was insoluble in cold sodium bicarbonate solution.

Anal. Found: N, 14.85.

The aqueous filtrate from above was acidified with concentrated hydrochloric acid and after chilling for several days 6.8 g. of succinylsulfathiazole was obtained, melting at 180–184°. It was soluble in cold sodium bicarbonate solution with evolution of carbon dioxide.

Condensations with two equivalents of 2-aminothiazole in acetone or one equivalent of 2-aminothiazole in sodium carbonate solution gave similar results.

Summary

A series of dicarboxylic acid derivatives of sulfonamides has been prepared for study as intestinal antiseptics.

Succinic, maleic and phthalic anhydrides condensed with the sulfonamides to give the monobasic acid amides I. Ethyl oxalate and ethyl malonate condensed with sulfathiazole, sulfadiazine and sulfaguanidine to give the ester amides IV, which were easily hydrolyzed by alkali to give the acid amides I, and a small amount of the diamides III. Esters of higher acids, such as ethyl glutarate, adipate and sebacate did not con-

(7) Adams, Long and Jeanes, THIS JOURNAL, 61, 2316 (1939).

dense with sulfathiazole even when heated at 160–170° for two hours.

Succinic acid condensed with the sulfonamides, when heated at a temperature of 150–170° for one to two hours, to give the anils II and 5–7% of the diamides IV. Hydrolysis of the anils II with 5–10% alkali gave the corresponding acid amides I. Condensation of glutaric, adipic and sebacic acids with the sulfonamides led to the isolation of the acid amides I and diamides III, in varying proportions.

p-Succinimidobenzenesulfonyl chloride condensed with 2-aminothiazole, under varying conditions, to give N^4-succinylsulfathiazole and an unidentified product.

GLENOLDEN, PA. RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

The Condensation of Some Secondary Aliphatic Alcohols with Benzene in the Presence of Aluminum Chloride

BY R. C. HUSTON AND I. A. KAYE[1]

Previous work in this Laboratory has shown that *t*-aliphatic alcohols condense with benzene and phenol in the presence of aluminum chloride to give the expected *t*-alkylbenzenes.[1a-3] Secondary aliphatic alcohols have been condensed with benzene too, but the nature of the products was not determined.[1a] The purpose of the present investigation was to extend the study of the condensation of secondary aliphatic alcohols with benzene, using aluminum chloride as catalyst, and to determine the nature of the products obtained.

s-Propyl, butyl, amyl, hexyl and nine of the *s*-heptyl alcohols were condensed with benzene. That isopropyl and *s*-butyl alcohols gave the expected hydrocarbons, cumene and *s*-butylbenzene, was shown by their monoacetamino derivatives whose melting points agreed with those in the literature.[4] The other monoalkylbenzenes were nitrated yielding the *p*-nitro derivatives which were then reduced to the amines. Phenols were prepared from the latter through the diazonium salts. The α-naphthylurethans of the phenols were then prepared. By comparison with the melting points of the α-naphthyl-urethans of known *t*-alkylphenols[2,3] and by mixed melting point determinations with these compounds, it was established that 2-methylbutanol-3, 2-methylpentanol-3, 2-methyl-hexanol-3 and 3-methylhexanol-4 gave the *t*-alkylbenzenes, 2-methyl-2-phenylbutane, 2-methyl-2-phenylpentane, 2-methyl-2-phenylhexane and 3-methyl-3-phenylhexane.

The *p*-hydroxy derivatives and their α-naphthylurethans of 2-phenylpentane, 3-phenylpentane, 2-phenylhexane, 3-phenylhexane, 3-methyl-2-phenylpentane, 2-methyl-4-phenylpentane, 2,2-dimethyl-3-phenylbutane, 2-phenylheptane, 3-phenylheptane, 4-phenylheptane, 2-methyl-4-phenylhexane, 2-methyl-5-phenylhexane, 3-methyl-2-phenylhexane, and 2,2-dimethyl-3-phenylpentane were synthesized. The condensation of pinacolyl alcohol with benzene gave an alkylbenzene which was converted into a phenol identical with synthesized 2,2-dimethyl-3-*p*-hydroxyphenylbutane. The other alcohols, pentanol-2, pentanol-3, hexanol-2, hexanol-3, 3-methylpentanol-2, 2-methylpentanol-4, heptanol-2, heptanol-3, heptanol-4,2-methylhexanol-4, 2-methylhexanol-5, 3-methylhexanol-2 and 2,2-dimethylpentanol-3 undoubtedly gave mixtures of monoalkylbenzenes such as might be formed by the splitting out of water and the condensation of the resulting olefin in either of the two possible positions. This formation of mixtures in the condensation of the *s*-amyl alcohols with benzene and phenol and in the condensation of the secondary hexylphenols has been observed by others[5,6,7] and it is quite possible that the same phenomenon occurs with the higher homologs. The formation of tertiary products in the condensation of *s*-aliphatic alcohols with methyl groups adjacent to the carbinol group has also been reported.[5,6,7]

(1) From a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(1a) Huston and Hsieh, THIS JOURNAL, **58**, 439 (1936).

(2) Huston and Hedrick, *ibid.*, **59**, 2001 (1937).

(3) Huston and Guile, *ibid.*, **61**, 69 (1939).

(4) Ipatieff and Schmerling, *ibid.*, **59**, 1056 (1937).

(5) Ipatieff, Pines and Schmerling, *J. Org. Chem.*, **5**, 253 (1941).

(6) Huston and Esterdahl, Master's Thesis, Michigan State College (1940).

(7) Huston and Curtis, *ibid.* (1941).