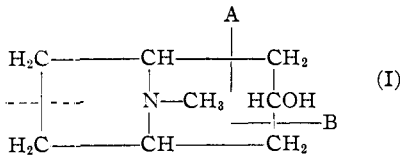
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

Antispasmodics. III. Diarylacetic Acid Esters of Some Pyridyl and Piperidyl Alkanols[1]

BY ROBERT R. BURTNER AND JOHN M. BROWN

In continuation of studies directed toward the synthesis of antispasmodics which exhibit a high degree of neurotrophic activity, typical of atropine, as well as a potent musculotropic effect, it was of interest to examine derivatives of some aminoalcohols which are related to the basic structural units of tropine.

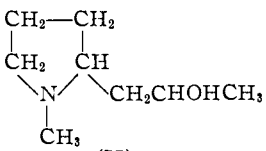
Hypothetical cleavage of tropine (I), as shown by the dotted line, gives rise to 1,2,6-trimethyl-4-



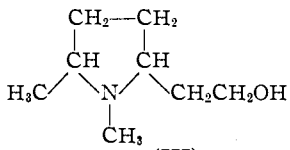
(I)

piperidinol. Esters of the latter with diphenylacetic and fluorene-9-carboxylic acids possessed marked spasmolytic properties, although the neurotropic activity was only about one-seventh that of atropine.[2]

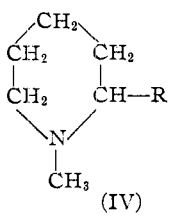
Cleavage as indicated by lines A and B yields 1-(N-methyl-α-pyrrolidyl)-2-propanol (II) and 1-(α,N-dimethyl-α'-pyrrolidyl)-2-ethanol (III), respectively. In view of the close chemical and pharmacological relationship between pyrrolidine and piperidine derivatives and the fact that the analogous piperidyl alkanols are more readily available, derivatives of the latter type (IV and V) were selected for study.



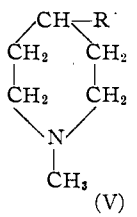
(II)



(III)



(IV)



(V)

R = CH_2CH_2OH, $CH_2CH_2CH_2OH$ or $CH_2CHOH—CH_3$

Pharmacological Part

The pharmacological studies were carried out in these Laboratories by Miss Lucile Hardenbrook, under the direction of Dr. W. E. Hambourger, and will be described in detail in a future paper. Spasmolytic activity was determined (1) on the isolated rabbit intestinal muscle by measuring the relaxation which the drug in question produced against (a) spasm induced by 5×10^{-5} acetylcholine bromide and (b) that induced by 10^{-3} barium chloride, and (2) on isolated guinea pig intestinal muscle by measuring relaxation produced against spasm induced by 3×10^{-5} histamine acid phosphate.

Activities against acetylcholine refer to a comparison of 16×10^{-6} "unknown" with 10^{-6} atropine where the latter produces immediate and complete relaxation of the muscle strip, to which degree of activity was arbitrarily assigned a value of 4+. Thus, a 4+ activity against acetylcholine means that the drug in question has $^1/_{16}$ the neurotropic activity of atropine.

Barium chloride and histamine activities refer to a comparison of the "unknown" with papaverine where the concentration of each is 5×10^{-5} against barium chloride and 3×10^{-5} against histamine, these concentrations of papaverine producing 4+ activity. Thus, a 4+ value against barium chloride and histamine means that the drug in question possesses musculotropic activity equivalent to that of papaverine in each instance.

It is to be understood that the values 1, 2, 3 and 4 do not represent an arithmetical progression of activity but rather an approximately geometrical one wherein the ratios of activity are obtained by regarding the given values as powers of 2. Thus, a 4+ compound possesses roughly twice the activity of a 3+ compound, 4 times the activity of a 2+ compound and 8 times the activity of a 1+ compound.

Experimental

Preparation of the Alkanols.—The pyridyl alkanols, with one exception,[3] were purchased from commercial sources[4] and distilled before use.

The piperidyl alkanols were obtained by low pressure hydrogenation of the corresponding pyridyl alkanols, using platinum oxide catalyst. These in turn were converted to the N-methyl compounds by heating under pressure with a mixture of formic acid and formaldehyde. The procedure is essentially that of Hess, Uibrig and Eichel,[5] who used it to prepare 1-(α-piperidyl)-2-propanol and 1-(α-N-methyl-piperidyl)-2-propanol. Following are specific examples of general procedures.

1-(α-Piperidyl)-3-propanol.—A solution of 27.4 g. (0.2 mole) of 1-(α-pyridyl)-3-propanol in 160 ml. of acetic acid (distilled over chromic acid) and 30 ml. of water was reduced at 50 lb. pressure in the presence of 0.7 g. of platinum oxide. In order to expedite reduction it was advisable to add 0.5 g. of fresh catalyst when about one-half of the theoretical amount of hydrogen had been absorbed. The reduction was usually complete in eight

(1) Presented before the Division of Medicinal Chemistry, 110th Meeting of the American Chemical Society, Chicago, Illinois, September 9, 1946.

(2) Burtner and Cusic, THIS JOURNAL, **65**, 262 (1943).

(3) 1-(α-Pyridyl)-2-propanol was prepared by the method of *Organic Syntheses*, **23**, 83 (1943).

(4) Reilly Tar and Chemical Corporation.

(5) Hess, Uibrig and Eichel, *Ber.*, **50**, 349 (1917).

TABLE I

Alkanol	Yield, %	B. p., °C.	mm.	$n^{25}D$	Formula	Nitrogen[a] analyses, % Calcd.	Found
1-(α-Piperidyl)-2-ethanol[b]	82	84–86	1.5	....	$C_7H_{15}ON$	...	...
1-(α-N-Methyl-piperidyl)-2-ethanol[b]	81	77–79	0.7	....	$C_8H_{17}ON$	...	...
1-(α-Piperidyl)-3-propanol	89	93–95	0.6	1.4863	$C_8H_{17}ON$	9.78	9.77
1-(α-Piperidyl)-3-propanol hydrochloride	..	130[c]		....	$C_8H_{18}ONCl$	19.7	19.4
1-(α-N-Methyl-piperidyl)-3-propanol	82	106–107	2.3	1.4819	$C_9H_{19}ON$	8.91	8.68
1-(α-N-Methyl-piperidyl)-3-propanol hydrochloride	..	138[c]		....	$C_9H_{20}ONCl$	18.30	18.04
1-(γ-Piperidyl)-2-ethanol	59[d]	125 46–47[c]	0.8	....	$C_7H_{15}ON$	10.84	10.41
1-(γ-Piperidyl)-2-ethanol hydrochloride	..	[e]		....	$C_7H_{16}ONCl$	21.4	21.0
1-(γ-N-Methyl-piperidyl)-2-ethanol	83	105	1.5	1.4750	$C_8H_{17}ON$	9.78	9.99
1-(γ-N-Methyl-piperidyl)-2-ethanol hydrochloride	..			....	$C_8H_{18}ONCl$	19.73	19.14
1-(γ-Piperidyl)-3-propanol	83	130–131 65[c]	1.5	....	$C_8H_{17}ON$	9.78	9.48
1-(γ-Piperidyl)-3-propanol hydrochloride	..	155[c]		....	$C_8H_{18}ONCl$	19.73	19.57
1-(γ-N-Methyl-piperidyl)-3-propanol	85	93–95	0.4	1.4761	$C_9H_{19}ON$	8.91	9.17
1-(γ-N-Methyl-piperidyl)-3-propanol hydrochloride	..	137[c]		....	$C_9H_{20}ONCl$	18.30	18.22

[a] In the case of the hydrochlorides, analytical data refer to chlorine analyses. [b] Ladenburg, *Ber.*, 24, 349 (1917). [c] Melting point. [d] Appreciable loss during distillation, due to dehydration and subsequent polymerization. [e] Material was too hygroscopic to permit satisfactory melting point determination.

to ten hours. The catalyst was removed and the solvent distilled under reduced pressure. The sirupy residue was then treated with an excess of 50% potassium hydroxide, saturated with potassium carbonate and extracted thrice with ether. The ethereal extract was dried over anhydrous potassium carbonate, the solvent removed and the residue distilled to give 26 g. of colorless oil (89%).

1-(α-N-Methyl-piperidyl)-3-propanol.—A solution of 77 g. (0.56 mole) of 1-(α-piperidyl)-3-propanol, 44.5 g. of 37% formaldehyde and 28.8 g. of 90% formic acid in 181 ml. of water was heated in a glass-lined bomb at 140° for five hours. The cold solution was then treated with an excess of 50% potassium hydroxide and worked up as described above to yield 70 g. of colorless oil (82%).

Neither of the γ-piperidyl alkanols nor their N-methyl derivatives was soluble in ether. In these instances the oily product was separated and distilled directly.

The hydrochlorides described in the table were prepared by treating a solution of the alkanol in anhydrous ether or *i*-propyl alcohol with a 5% excess of absolute alcoholic hydrogen chloride. Subsequent addition of anhydrous ether precipitated the hydrochlorides in such pure form that crystallization was usually unnecessary.

Preparation of the Acid Chlorides.—The acid chlorides were prepared by the use of thionyl chloride in carbon tetrachloride solution. Diphenylacetyl chloride was purified by vacuum distillation before using. Fluorene-9-carboxylic acid chloride, being unstable at distillation temperatures, was employed in crude form immediately upon removal of solvent and unreacted thionyl chloride.

Synthesis of the Esters.—The esters were prepared by interaction of the alkanols and acid chlorides in benzene solution at steam-bath temperature for three and one-half to five hours. Yields varied widely, a fact of little significance in the present work, since our immediate objective was the preparation of materials in quantities sufficient for pharmacological evaluation. The following syntheses will serve as examples of the technique used.

TABLE II

HYDROCHLORIDES OF DIPHENYLACETIC ACID ESTERS

Alkanol	M. p., °C.	Crystallization solvent	Formula	Nitrogen, % Calcd.	Found	Spasmolytic activity: Acetylcholine[a]	Barium[a] chloride	Histamine[a]	L. D.^{50} g./kg.[b]
1-(α-Pyridyl)-2-ethanol	83–85	*i*-PrOH + EtOAc	$C_{21}H_{20}O_2NCl$	3.96	3.67	3½	4	4	0.67
1-(α-Pyridyl)-2-propanol	114[c]	MeEt ketone	$C_{22}H_{22}O_2NCl$	3.81	3.70	3	4	4	0.44
1-(α-Pyridyl)-3-propanol	96–98	*i*-PrOH + EtOAc	$C_{22}H_{22}O_2NCl$	3.81	3.62	2½	3½	3	0.50
1-(γ-Pyridyl)-2-ethanol	[d]	[e]	$C_{21}H_{20}O_2NCl$	3.96	4.40	3	3½	2½	<0.05
1-(γ-Pyridyl)-3-propanol	153–155	[f]	$C_{22}H_{22}O_2NCl$	3.81	3.60	3	3½	3½	0.8
1-(α-N-Methyl-piperidyl)-2-ethanol	152–153	*i*-PrOH + EtOAc	$C_{22}H_{28}O_2NCl$	3.75	3.62	3½	4	3½	0.15
1-(α-N-Methyl-piperidyl)-2-propanol	[d]	[e]	$C_{23}H_{30}O_2NCl$	3.61	3.76	3	4	4	0.05
1-(α-N-Methyl-piperidyl)-3-propanol	103–105	*i*-PrOH + EtOAc	$C_{23}H_{30}O_2NCl$	3.61	3.39	2½	4	2½	0.10
1-(γ-N-Methyl-piperidyl)-2-ethanol	171–172	*i*-PrOH + EtOAc	$C_{22}H_{28}O_2NCl$	3.75	3.71	3½	4	4	0.13
1-(γ-N-Methyl-piperidyl)-3-propanol	110–111	*i*-PrOH + EtOAc	$C_{23}H_{30}O_2NCl$	3.61	3.66	4	3½	4	0.07

[a] For comparative activities of atropine and papaverine, see text. [b] L. D.^{50} for atropine = 0.24; for papaverine = 0.35. [c] Owing to hygroscopicity, this m. p. may be low. [d] Hygroscopicity too great for m. p. determination. [e] Could not be recrystallized from any of several solvents. [f] Not recrystallized; precipitated as crystalline solid on treatment of the base with alcoholic hydrochloric acid. Sample recrystallized from dioxane showed no change in m. p.

TABLE III

HYDROCHLORIDES OF FLUORENE-9-CARBOXYLIC ACID ESTERS[a]

Alkanol	Formula	Nitrogen, % Calcd.	Found	Spasmolytic activity—Acetylcholine	Barium chloride	Histamine	L. D.$_{50}$ g./kg.
1-(α-Pyridyl)-2-ethanol	$C_{21}H_{18}O_2NCl$	3.98	3.52	2	2½	1	>1.0
1-(α-Pyridyl)-2-propanol	$C_{22}H_{20}O_2NCl$	3.83	3.75	2½	3½	4	>1.0
1-(α-Pyridyl)-3-propanol	$C_{22}H_{20}O_2NCl$	3.83	3.74	2½	1	3½	0.40
1-(γ-Pyridyl)-2-ethanol	$C_{21}H_{18}O_2NCl$	3.98	4.02	3	3	4	0.63
1-(γ-Pyridyl)-3-propanol[b]	$C_{22}H_{20}O_2NCl$	3.83	3.54	2	3	3½	1.0
1-(α-N-Methyl-piperidyl)-2-ethanol	$C_{22}H_{26}O_2NCl$	3.77	3.34	3	3½	3½	0.20
1-(α-N-Methyl-piperidyl)-2-propanol	$C_{23}H_{28}O_2NCl$	3.63	3.43	4	4	4	0.05
1-(α-N-Methyl-piperidyl)-3-propanol	$C_{23}H_{28}O_2NCl$	3.63	3.19	3	3	4	<0.05
1-(γ-N-Methyl-piperidyl)-2-ethanol	$C_{22}H_{26}O_2NCl$	3.77	3.34	3½	4	4	0.13
1-(γ-N-Methyl-piperidyl)-3-propanol	$C_{23}H_{28}O_2NCl$	3.63	3.38	3½	2½	4	0.07

[a] With one exception, these compounds could not be recrystallized from any of several solvents; and their hygroscopicity was too great for m. p. determination. They generally precipitated as oils which granulated on standing and were purified by washing with ether and reprecipitation where necessary. [b] Recrystallized from *i*-PrOH + EtOAc; m. p. 150–152°.

1-(γ-N-Methyl-piperidyl)-2-ethyl Diphenylacetate Hydrochloride.—To a solution of 34.5 g. (0.15 mole) of diphenylacetyl chloride in 100 ml. of dry benzene was added a solution of 20.1 g. (0.14 mole) of 1-(γ-N-methyl-piperidyl)-2-ethanol in 100 ml. of benzene. The resulting mixture was heated on the steam-bath for five hours. Following the heating period, 100 ml. more of benzene was added and the mixture was made alkaline by shaking with a solution of 16 g. of sodium hydroxide in 200 ml. of water. The benzene layer was separated and the aqueous raffinate extracted with 200 ml. of fresh benzene. The combined extracts were washed with water, dried over sodium sulfate and filtered. Subsequent removal of solvent on the water bath at 60° under water pump vacuum left a dark oily residue weighing 51 g.

The residue was taken up in 510 ml. of dry ether and treated with Darco, and a small amount of insoluble material was filtered out. Upon addition of the theoretical amount of absolute alcoholic hydrochloric acid, the hydrochloride was precipitated as well-defined white crystals.

The crystals were washed by decantation with dry ether, recovered on a Büchner funnel, washed additionally thereon and dried *in vacuo* over sodium hydroxide to give 44.8 g. of material with m. p. 168–170°.

Upon recrystallization from 198 ml. of *i*-propanol plus 198 ml. of ethyl acetate, treating with Darco in process, there was obtained 25 g. of colorless product m. p. 171–172°. The yield was 48%.

Anal. Calcd. for $C_{22}H_{28}O_2NCl$: N, 3.75; Cl, 9.48. Found: N, 3.71; Cl, 9.38.

1-(α-Pyridyl)-2-propyl Fluorene-9-carboxylate Hydrochloride.—A mixture of 21 g. (0.1 mole) of fluorene-9-carboxylic acid, 30 g. (0.25 mole) of thionyl chloride and 65 ml. of dry carbon tetrachloride was refluxed for one and one-half hours, during which time complete solution was effected. Solvent and excess thionyl chloride were removed on the water-bath at 60° under water pump vacuum, and the semi-solid residue was immediately dissolved in 50 ml. of dry benzene.

To this solution of the crude fluorene-9-carboxylic acid chloride was added a solution of 13.7 g. (0.1 mole) of 1-(α-pyridyl)-2-propanol in 50 ml. of benzene, and the resulting mixture was heated for three and one-half hours on the steam-bath. The mixture was then made alkaline by shaking with a solution of 8 g. of sodium hydroxide in 100 ml. of water, whereupon the reaction product was dissolved.[6] The benzene layer was separated and the aqueous raffinate extracted with 100 ml. of fresh benzene. The combined benzene extracts were then worked up as above to give 33.2 g. of brown oily basic ester.

The ester was taken up in 400 ml. of dry ether; and a small amount[7] of insoluble material was filtered out, treating with Darco in process. Addition of one equivalent of absolute alcoholic hydrogen chloride precipitated the hydrochloride as a viscous, semi-solid material which failed to crystallize even after four weeks.

Reprecipitation of the base with 10% sodium carbonate solution gave 19.5 g. of an orange viscous oil, which was dissolved in 300 ml. of dry ether and treated with absolute alcoholic hydrogen chloride as above. The hydrochloride again came down in semi-solid form.

The white semi-solid product was thereupon washed repeatedly by decantation with fresh dry ether and dried *in vacuo* over sodium hydroxide to give 14.5 g. of colorless amorphous solid. Hygroscopicity was too great for melting point determination. The yield was 40%.

Anal. Calcd. for $C_{22}H_{20}O_2NCl$: N, 3.83; Cl, 9.69. Found: N, 3.75; Cl, 9.46.

During the course of this work it was noted that 1-(γ-pyridyl)-2-ethanol and the corresponding piperidyl compound are somewhat unstable at elevated temperatures, particularly in the presence of mineral acids. Indeed, it was found that the 1-(γ-pyridyl)-2-ethanol ester of diphenylacetic acid could not be prepared by the method given above, because of this phenomenon. Instead, the following procedure was used.

1-(γ-Pyridyl)-2-ethyl Diphenylacetate Hydrochloride.—To a solution of 25.3 g. (0.11 mole) of diphenylacetyl chloride in 50 ml. of dry benzene was added a solution of 12.3 g. (0.1 mole) of 1-(γ-pyridyl)-2-ethanol plus 19.6 g. (0.17 mole) of N-ethylmorpholine in 50 ml. of benzene. The resulting mixture was heated on the steam-bath for five hours. Following the heating period, 100 ml. more of benzene was added and the mixture was made alkaline by shaking with a solution of 8 g. of sodium hydroxide in 100 ml. of water. A small amount (less than 3.0 g.) of tar was found and discarded. The benzene layer was separated and the aqueous raffinate extracted with 100 ml. of fresh benzene. The combined benzene extracts were then worked up as above to give 23.0 g. of red-brown oily ester.

Solution of the ester in dry ether, treatment with Darco, filtration and precipitation with absolute alcoholic hydrochloric acid in the usual way gave an orange-brown semi-solid hydrochloride which failed to crystallize after three days.

The plastic mass was washed repeatedly by decantation with fresh dry ether and dried *in vacuo* over sodium hy-

(6) Occasionally the reaction product came out as a relatively insoluble "glass" or "resin." In such cases the benzene–alkali supernatant was decanted and set aside and the "glass" was resolved by warming briefly on the steam-bath with 1–2 ml. (sufficient to ensure acidity) of concentrated hydrochloric acid. The solubilized reaction product was then recombined with the benzene–alkali liquors and extracted in the usual way.

(7) Usually less than 1.0 g. However, in the preparation of the 1-(α-N-methyl piperidyl)-3-propanol and 1-(γ-N-methyl piperidyl)-2-ethanol esters of fluorene-9-carboxylic acid, there was filtered out at this point 3.0 g. and 2.8 g., respectively, of an amorphous tan powder.

droxide to give 6 g. of a tan amorphous solid. Hygroscopicity was too great for melting point determination. The yield was 17%.

Anal. Calcd. for $C_{21}H_{20}O_2NCl$: N, 3.96; Cl, 10.02. Found: N, 4.40; Cl, 10.93.

Summary

A series of twenty pyridyl and N-methylpiperidyl alkanol esters of diphenylacetic and fluorene-9-carboxylic acids was prepared and studied *in vitro* for spasmolytic action. The diphenylacetic acid esters appears generally more active than the corresponding fluorene-9-carboxylic acid esters, particularly against spasm induced by acetylcholine and barium chloride; the latter are, however, less toxic. Reduction and N-methylation of the pyridine ring usually increases both the activity and toxicity. The most promising spasmolytic of the series is 1-(α-pyridyl)-2-ethyl diphenylacetate hydrochloride.

CHICAGO, ILLINOIS RECEIVED JULY 15, 1946

[CONTRIBUTION FROM THE APPLIED SCIENCE RESEARCH LABORATORY OF THE UNIVERSITY OF CINCINNATI]

Aliphatic Trienes—A Synthesis from Acetylene-diols

BY R. E. WERNER[1] AND W. B. REYNOLDS

Aliphatic acetylene-diols of the type R—CH(OH)—C≡C—CH(OH)—R, which can be prepared readily either by treating the acetylene di-Grignard reagent with two moles of aliphatic aldehyde or by treating aldehyde with acetylene under the catalytic influence of copper acetylide, can be conveniently semi-hydrogenated to the corresponding olefin-diols.[2] During the course of a study of synthetic drying oils in this Laboratory it became desirable to synthesize certain aliphatic trienes. The acetylene-diols were chosen as convenient starting materials for these syntheses.

Several attempts have been made to dehydrate the olefin-1,4-diols produced by semi-hydrogenation of products obtained when acetylene dimagnesium bromide is caused to react with aliphatic carbonyl compounds. In every instance reported, however, the product has been a substituted dihydrofuran.[3] Bourguel and Rambaud[4] reported the synthesis of 2,5-dimethylhexatriene through the dehydration of 2,5-dimethyl-2,5-dihydroxy-3-hexene. However, it was later shown by Zalkind and Bukhovets[5] that the product thought by those investigators to be the olefin-diol was, in reality, the acetylene-diol. Consequently, the product they believed to be the triene was actually a divinylacetylene derivative. The true 2,5-dimethylhexatriene has recently been synthesized by Kharasch, Nudenberg and Sternfeld[6] through the condensation of β-methylallyl chloride with sodamide in liquid ammonia.

We have found that the difficulties attending the dehydration of the olefin-1,4-glycols are avoided by replacing the hydroxyl groups by chlorine through the action of anhydrous hydrogen chloride in petroleum ether solution, and dehydrohalogenation by means of pyridine. 3,5,7-Decatriene, for example, was prepared by the following series of reactions

$$2H_3C—CH_2—CH_2CHO + BrMg—C\equiv C—MgBr \longrightarrow C_3H_7—CH(OH)—C\equiv C—CH(OH)—C_3H_7 \quad (1)$$

$$C_3H_7—CH(OH)—C\equiv C—CH(OH)—C_3H_7 + H_2 \xrightarrow{Ni} C_3H_7—CH(OH)—CH=CH—CH(OH)—C_3H_7 \quad (2)$$

$$C_3H_7—CH(OH)—CH=CH—CH(OH)—C_3H_7 \xrightarrow{HCl} C_3H_7—CHCl—CH=CH—CHCl—C_3H_7 \quad (3)$$

$$C_3H_7—CHCl—CH=CH—CHCl—C_3H_7 \xrightarrow{pyridine} C_2H_5—CH=CH—CH=CH—CH=CH—C_2H_5 \quad (4)$$

2,5-Dimethyl-1,3,5-hexatriene was prepared by the same series of reactions starting with acetone and the acetylene di-Grignard. This product formed a crystalline adduct with maleic anhydride which melted at 114–115°, confirming the value reported for the same product by Kharasch, Nudenberg and Sternfeld.[6]

Experimental

Acetylene Dimagnesium Bromide.—This was prepared according to the method of Jozitsch[7] by passing acetylene for five hours at 150 ml./min. through a well-stirred solution of 3 moles of ethylmagnesium bromide in 1500 ml. of absolute ether contained in a 3-liter, 3-necked flask equipped with a mercury-sealed stirrer, reflux condenser, dropping funnel and gas inlet tube.

4,7-Dihydroxy-5-decyne.[8]—After the acetylene di-Grignard had stood overnight, 265 ml. (217 g., 3 moles) of freshly distilled butyraldehyde was added, with good agitation, over the course of one and one-half hours. Stirring was continued for another hour and the mixture

(1) This article is taken from a portion of the thesis submitted by R. E. Werner in partial fulfillment of the requirements for the degree of Doctor of Science. The work was carried out during the tenure of a fellowship supported by the Ault and Wiborg Division of Interchemical Corporation.

(2) Zalkind and Bezsonova, *J. Phys. Chem.*, U. S. S. R., **53**, I, 284 (1921); *C. A.*, **18**, 2327 (1923); Zalkind, *Ber.*, **56B**, 187 (1923); *ibid.*, **60B**, 1125 (1927).

(3) Blomquist and Marvel, THIS JOURNAL, **55**, 1658 (1933).

(4) Bourguel and Rambaud, *Bull. soc. chim.*, [4] **47**, 173 (1930).

(5) Zalkind and Bukhovets, *J. Gen. Chem.*, U. S. S. R., **7**, 2417 (1937); *C. A.*, **32**, 2086 (1938); *cf.* Zalkind, THIS JOURNAL, **63**, 2282 (1941); Johnson and Johnson, *ibid.*, **62**, 2615 (1940); **63**, 2282 (1941).

(6) Kharasch, Nudenberg and Sternfeld, THIS JOURNAL, **62**, 2034 (1940).

(7) Jozitsch, *Bull. soc. chim.*, [3] **32**, 552 (1904); *cf.* Dupont, *Ann. chim. phys.*, [8] **30**, 485 (1913).

(8) Marvel and Williams, THIS JOURNAL, **61**, 2714 (1939).