by hot acetylation with sodium acetate and acetic anhydride.

N-Methyl-L-glucosaminic Acid.—Fifty grams of N-methyl-L-glucosaminic acid nitrile was dissolved in 100 cc. of concentrated hydrochloric acid (d. 1.19) with cooling. The solution was then evaporated under reduced pressure to a sirup. All but traces of the hydrochloric acid were removed by alternate solution in water and evaporation under reduced pressure. The sirup was dissolved in 200 cc. of water, 95 g. of barium hydroxide octahydrate added, and the solution boiled until the odor of ammonia could no longer be detected. The barium ion was precipitated exactly by the addition of sulfuric acid. Activated carbon was added and the hot mixture filtered. The solution was treated with lead carbonate until it no longer effervesced. Decolorizing carbon was added again, the solution filtered, and evaporated under reduced pressure to 100 cc. It was allowed to stand in the ice-box overnight. The separated lead chloride was removed by filtration. The solution was warmed and treated with silver carbonate to remove the remainder of the chloride ion and the mixture filtered. The lead and silver ions were precipitated with hydrogen sulfide and the colorless liquid evaporated under reduced pressure at a temperature below 50° to a thin sirup. Absolute ethanol was added and the evaporation continued until a heavy crop of crystalline acid formed. The crystalline material was removed by filtration. More crystals were obtained by the addition of ethanol to the mother liquor and further evaporation; yield 32 g., m. p. 234–236° (dec.), $[\alpha]^{25}D$ −3.0° (*c* 4.1, water); no mutarotation. Pure material was obtained on two recrystallizations from water–ethanol; m. p. 236° (dec.), $[\alpha]^{24}D$ −4.6° (*c* 4.0, water); $[\alpha]^{29}D$ −3.0° (initial, extrapolated) → −9.1° (final) (*c* 10.8, 2.5% hydrochloric acid). These constants are in agreement (opposite sign) with those cited by Votoček and Lukeš[7] for the enantiomorph and with the melting point cited by Folkers and co-workers.[4]

The substance is soluble in water, very slightly soluble in ethanol and is insoluble in ether.

Anal. Calcd. for $C_7H_{15}O_6N$: C, 40.19; H, 7.23; N, 6.70. Found: C, 40.22; H, 7.25; N, 6.64.

Acknowledgment.—We are indebted to Mr. W. J. Polglase for the analytical data recorded.

Summary

1. An effective method for the preparation of N-methyl-L-glucosaminic acid is reported.

2. L-Arabinosyl-N-methylamine and N-methyl-L-glucosaminic acid nitrile (and its pentaacetate) have been synthesized in crystalline form.

3. Postulations are made concerning the nature of the isomeric forms of D-gluconic acid nitrile.

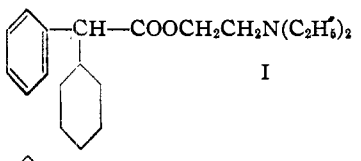
COLUMBUS, OHIO RECEIVED AUGUST 12, 1946

[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

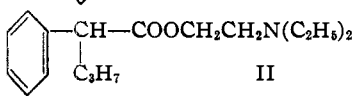
Antispasmodics. Derivatives of 1-Phenylcycloparaffincarboxylic Acids

BY ARTHUR W. WESTON

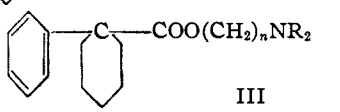
Basic alkyl esters of substituted acetic acids have been studied extensively in a search for a synthetic antispasmodic drug which would combine both a musculotropic and neurotropic action within the same molecule.[1] Two compounds possessing this dual activity to an appreciable degree are Trasentin-6H (I) and Propavine (II).



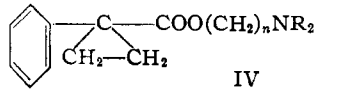
I



II



III



IV

In an effort to find a potent antispasmodic drug, basic alkyl esters of 1-phenylcyclohexanecarboxylic acid (III) and 1-phenylcyclopropanecarboxylic acid (IV), which are somewhat related structurally to I and II, were synthesized and examined for their antispasmodic activity. For purposes of comparison, some basic alkyl thioesters and amides of these acids were also prepared.

After this work was completed, a report[2] on the investigation of a series of compounds derived from 1-phenylcyclohexanecarboxylic acid appeared. One of the esters prepared in the present work, β-diethylaminoethyl 1-phenylcyclohexanecarboxylate, was described therein.

1-Phenylcyclohexanenitrile, one of the starting materials, was obtained by a modification of the published method[3] in which phenylacetonitrile was condensed with pentamethylene bromide in the presence of sodamide. By employing a relatively large volume of solvent, it was found that the tendency for intermolecular condensation was diminished. This resulted in an increased yield of the 1-phenylcyclohexanenitrile. Whether higher dilutions would have still further improved this conversion was not investigated. Hydrolysis of the nitrile was accomplished with 48% hydrobromic acid. Case[3] reported a 22.2% over-all yield of 1-phenylcyclohexanecarboxylic acid from phenylacetonitrile. By the present method a 52% yield was realized.

The 1-phenylcyclopropanenitrile was prepared, according to the directions of Knowles and Cloke[4] as modified by Case,[3] from phenylacetonitrile and

(1) For recent reviews see Raymond, *J. Am. Pharm. Assoc. Sci. Ed.*, **32**, 249 (1943); Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

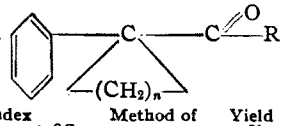
(2) Rubin and Wishinsky, THIS JOURNAL, **68**, 828 (1946).

(3) Case, *ibid.*, **56**, 715 (1934).

(4) Knowles and Cloke, *ibid.*, **54**, 2028 (1932).

TABLE I

BASIC ALKYL ESTERS OF 1-PHENYLCYCLOPROPANE- AND 1-PHENYLCYCLOHEXANECARBOXYLIC ACIDS AND HYDROCHLORIDES[a]



AP[b] no.	n	R	B. p., °C.	Mm.	Ref. index n_D	t, °C.	Method of prepn.	Yield %
53	2	$OCH_2CH_2N(C_2H_5)_2$	.....	..	....	..	Ib	76[d]
68	5	$OCH_2CH_2N(C_2H_5)_2$	155–157	2	1.5110	25	Ia	80
							II	70[d]
139	5	$OCH_2CH_2N(C_2H_5)_2$	.....	..	....	..	...	..
143	2	$SCH_2CH_2N(C_2H_5)_2$	164–165	2	1.5398	26	Ia	94
155	5	$SCH_2CH_2N(C_2H_5)_2$	185–186	2	1.5449	23	Ia	78
140	5	$NHCH_2CH_2N(C_2H_5)_2$	202–203	3	1.5280	24	Ia	94
144	2	$OCH_2CH_2NHCH_2C_6H_5$	.....	..	....	..	Ic	70[d]
142	2	$OCH_2CH_2CH_2NC_4H_8O$[g]	173–175	2	1.5193	26	IV	73
141	5	$OCH_2CH_2CH_2NC_4H_8O$[g]	202–203	2	1.5238	26	III	92
119	5	$OCH_2C(CH_3)_2CH_2NC_4N_8O$[g]	.....[h]	..	....	..	Ia	88
113	5	$OCH_2(CH_2)_4CH_2NC_4H_8O$[g]	228–230	4	1.5166	24	IV	86
							Ia	87

AP[b] no.	HCl M. p., °C.	Cryst. solvent[c]	Formula	Nitrogen, % Base Calcd.	Base Found	Hydrochloride Calcd.	Hydrochloride Found
53	132–133	Et	$C_{16}H_{23}NO_2 \cdot HCl$	..	..	4.70	4.73
68	162–163	Et	$C_{19}H_{29}NO_2(HCl)$	4.62	4.65	4.12	4.12
139	101.5–102[e]	AA-E	$C_{19}H_{29}NO_2 \cdot CH_3I$[a]	..	..	3.15	3.16
143	137–138	Et	$C_{16}H_{23}NOS(HCl)$[f]	5.05	5.04	4.46	4.40
155	140–141	Et	$C_{19}H_{19}NOS(HCl)$	4.39	4.16	3.94	3.90
140	166.5–167	AA-E	$C_{19}H_{29}N_2O(HCl)$	9.30	9.34	8.28	8.14
144	171–172	AA	$C_{19}H_{27}NO_2 \cdot HCl$	..	..	4.22	4.16
142	168–169	AA	$C_{17}H_{23}NO_3(HCl)$	4.84	4.86	4.30	4.38
141	174–175	AA	$C_{20}H_{29}NO_3(HCl)$	4.23	4.25	3.81	3.96
119	180–181	AA	$C_{22}H_{33}NO_5(HCl)$	3.90	3.97	3.54	3.53
113	121–122	Et	$C_{23}H_{35}NO_5(HCl)$	3.75	3.79	3.42	3.47

[a] Compound 139 is the methiodide. [b] Antispasmodic code number. [c] Legend: Et, ethyl acetate; AA, absolute alcohol; E, ether. [d] Crude yield. [e] Decomposition. [f] Sulfur anal., calcd., 10.21; found: 10.32. [g] NC_4H_8O represents the morpholino group. [h] M. p., 53–54° (dil. alc.).

ethylene dibromide. Alcoholic potassium hydroxide gave the amide which was then converted to the acid by refluxing with concentrated hydrochloric acid.

The oxygen esters were synthesized by a variety of methods: I, by condensation of the acid chloride (a) with excess of the aminoalcohol, (b) with one equivalent of the aminoalcohol, (c) with the aminoalcohol hydrochloride; II, by heating the acid with the dialkylaminoalkyl halide[5]; III, by heating the potassium salt of the acid with the dialkylaminoalkyl halide and IV, by amination of the corresponding bromoalkyl esters.

One of the bromoalkyl esters, the ω-bromohexyl 1-phenylcyclohexanecarboxylate, was made and aminated by the procedure recently described[6] for preparing the corresponding ω-morpholinohexyl diphenylacetate. However, better yields were obtained in the present work.

The amide and thioesters were formed by the reaction of the acid chloride with excess of the dialkylaminoalkylamine and the dialkylaminoalkyl mercaptan, respectively (Method Ia).

The various methods of preparing the esters are described in the experimental section.

(5) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(6) Cheney and Bywater, THIS JOURNAL, **64**, 970 (1942).

The pertinent data on the free basic esters and their hydrochlorides are recorded in Table I.

In Table II some of the pharmacological results[7] obtained with the compounds prepared in this in-

TABLE II

TOXICITIES AND ANTISPASMODIC ACTIVITIES OF PRODUCTS

AP[a] no.	LD_{50} mg./kg.	Antispasmodic activity against Acetylcholine	$BaCl_2$
53	225	1/250	1/8
68	170	1/15	1.0
139	100	1/50	1/2
143	220	1/15	2.0
155	140	1/50	2.0
140	200	<1/100	1.0
144	220	<1/1000	1.0
142	350	<1/100	1.0
141	250	<1/75	1.0
119	>800	<1/60	1.0
113	220	1/10–1/15	2.0
Atropine	250	1.0	...
Papaverine	225	1/1000	1.0
Trasentin	270	1/25	1.0

[a] Antispasmodic code number.

(7) The author is grateful to Dr. R. K. Richards and Mr. K. E. Kueter of the Pharmacological Research Department of these laboratories for this preliminary report of their experiments.

vestigation are listed. For comparison, the corresponding data on atropine, papaverine and Trasentin are included.

The toxicities were determined by intraperitoneal injection of an aqueous solution of the hydrochlorides in mice. The antispasmodic activity was evaluated against acetylcholine and barium chloride induced spasms in the isolated rabbit intestine using atropine and papaverine, respectively, as the standards. The values given, therefore, are fractions or multiples of the activity of the standard.

The two most active compounds in this series are AP-113, ω-morpholinohexyl 1-phenylcyclohexane carboxylate and AP-143, β-diethylaminoethyl 1-phenylcyclopropanethioxarboxylate. Both substances are more active than papaverine and, in addition, possess a substantial neurotropic activity. Several of these compounds are still under investigation.

Experimental

1-Phenylcyclopropanenitrile.[3,4]—This nitrile, b. p. 102–103° at 3 mm., was obtained in a 51% yield.

1-Phenylcyclopropanecarboxylic Acid.—Hydrolysis of the above nitrile with methyl alcoholic potassium hydroxide gave the amide which by refluxing with concentrated hydrochloric acid was converted to the free acid, m. p. 85–87°. After crystallization from Skellysolve B the material melted at 87–88°. The reported m. p. is 86–87°.[3,4]

1-Phenylcyclopropanecarboxylic Acid Chloride.—Treatment of 65 g. (0.4 mole) of the acid with 72 g. (0.6 mole) of thionyl chloride in the usual manner gave 71.2 g., a 98% yield of colorless oil, b. p. 98–100° at 5 mm., $n^{25}D$ 1.5458.

Anal.[8] Calcd. for $C_{10}H_9OCl$: C, 66.50; H, 5.03. Found: C, 67.07; H, 5.19.

1-Phenylcyclohexanenitrile.—Fifty-five grams (2.2 moles) of sodium was converted into sodamide by the usual procedure.[9] Following the addition of 500 cc. of dry ether, the ammonia was allowed to evaporate. To the resulting suspension of sodamide, 129 g. (1.1 moles) of phenylacetonitrile was added slowly with stirring. This mixture was refluxed four hours, then diluted with 1500 cc. more of dry ether. The addition of 230 g. (1.1 mole) of pentamethylene bromide[10] was followed by fourteen hours of refluxing. Cold water was then cautiously added, the insoluble material removed by filtration and the ether layer dried and concentrated. Distillation of the residual oil gave 118 g. (58%) of product, b. p. 125–127° at 3 mm., $n^{26}D$ 1.5330.

Anal. Calcd. for $C_{12}H_{15}N$; N, 7.56. Found: N, 7.64.

1-Phenylcyclohexanecarboxylic Acid.—A mixture of 67 g. (0.37 mole) of the above nitrile and 250 cc. of 48% hydrobromic acid was refluxed for eighty hours. The solid obtained by filtering the cooled reaction mixture was dissolved in ether which was then extracted with 10% sodium hydroxide. The acid which was liberated by acidifying the alkaline extracts was collected by filtration, washed with water and dried. It weighed 66 g. (89%) and melted at 121–123°. The pure acid had m. p. 123–124° after crystallization from Skelly B. The literature values are 121°[3] and 123–124°.[2]

1-Phenylcyclohexanecarboxylic Acid Chloride.—Obtained as described for the cyclopropane derivative in an almost quantitative yield, b. p. 130–131° at 4 mm., $n^{23}D$ 1.5477. On standing this oil became a low melting solid.

Anal. Calcd. for $C_{13}H_{15}OCl$: C, 70.10; H, 6.79. Found: C, 70.20; H, 6.75.

Method Ia. β-Diethylaminoethyl 1-Phenylcyclopropanethiocarboxylate.—To a benzene solution of 8.2 g. (0.06 mole) of β-diethylaminoethyl mercaptan,[11] 5.4 g. (0.03 mole) of 1-phenylcyclopropanecarboxylic acid chloride was added slowly. An immediate reaction ensued accompanied by the separation of a solid. After standing overnight, the β-diethylaminoethyl mercaptan hydrochloride (4.7 g.) was recovered by filtration and washed with benzene. The benzene filtrates were combined, washed with water, dried, concentrated and the residue distilled. The product boiled at 164–165° at 2 mm., $n^{26}D$ 1.5398, and amounted to 7.8 g., a 94% yield. The hydrochloride, prepared in the usual manner, melted at 137–138° after crystallization from ethyl acetate.

Method Ib. β-Diethylaminoethyl 1-Phenylcyclopropanecarboxylate Hydrochloride.—By refluxing a benzene solution of 7.2 g. (0.04 mole) of 1-phenylcyclopropanecarboxylic acid chloride with 4.7 g. (0.04 mole) of β-diethylaminoethanol, a gelatinous precipitate first formed but this disappeared on further heating. After several hours, the clear solution was cooled and the resulting hygroscopic solid filtered and washed with ether. The product weighed 9.0 g. (76%) after one crystallization from ethyl acetate. Recrystallization gave 7.6 g., m. p. 132–133°. Further purification did not change the melting point.

Method Ic. β-Benzylaminoethyl 1-Phenylcyclopropanecarboxylate Hydrochloride.—A suspension of β-benzylaminoethanol hydrochloride, prepared by passing hydrogen chloride gas into 2.5 g. (0.017 mole) of the amine in 50 cc. of toluene, was refluxed and stirred with 3.0 g. (0.017 mole) of 1-phenylcyclopropanecarboxylic acid chloride until a clear solution resulted. The solvent was then removed and the residue crystallized from absolute alcohol–ether whereby 3.9 g. (70%) of material, m. p. 165–167°, was obtained. Two recrystallizations from absolute alcohol gave 3.3 g. of pure material, m. p. 171–172°.

Method II. β-Diethylaminoethyl 1-Phenylcyclohexanecarboxylate.—A solution of 6.12 g. (0.03 mole) of 1-phenylcyclohexanecarboxylic acid and 4.2 g. (0.03 mole) of β-diethylaminoethyl chloride in 30 cc. of isopropyl alcohol was refluxed for sixteen hours. The product which separated, on cooling the alcohol solution, was filtered and washed with ether. It weighed 7.1 g., a 70% yield. By crystallization from ethyl acetate, 5.9 g., m. p. 160–161.5°, was obtained. The pure material had m. p. 162–163°. Rubin and Wishinsky[2] reported m. p. 159–160°.

Using Method Ia, the free base b. p. 155–157° at 2 mm., $n^{25}D$ 1.5110, was obtained in an 80% yield.

By the addition of a slight excess of methyl iodide to the free base, the methiodide was formed. It solidified on standing and melted at 101.5–102° after crystallization from an absolute alcohol–ether mixture.

Method III. γ-Morpholinopropyl 1-Phenylcyclohexanecarboxylate.—A methyl alcohol solution of 10.2 g. (0.05 mole) of 1-phenylcyclohexanecarboxylic acid was neutralized with a methyl alcohol solution of potassium hydroxide using phenolphthalein as the indicator. The potassium salt obtained by concentrating the resulting solution was dried, then suspended in 150 cc. of dry toluene. After the addition of 8.8 g. (0.054 mole) of γ-morpholinopropyl chloride,[12] the mixture was refluxed and stirred for fifteen hours. The basic product was extracted with acid, liberated by alkali then taken up in ether. By concentrating the dried ether extracts and distilling the residue, 15.3 g. (92%) of the ester boiling at 202–203° at 2 mm., $n^{25}D$ 1.5238 was obtained.

The hydrochloride melted at 174–175° on crystallization from absolute alcohol.

Method IV. ω-Bromohexyl 1-Phenylcyclohexanecarboxylate.—A mixture of the potassium salt, prepared as in the previous example from 87.7 g. (0.43 mole) of 1-phenylcyclohexanecarboxylic acid, and 375 g. (1.54 moles) of hexamethylene dibromide was stirred and heated on the

(8) A better analysis was not obtainable due to the instability of the compound.

(9) Vaughn, Vogt and Niewland, THIS JOURNAL, **56**, 2120 (1934).

(10) "Organic Syntheses," Coll. Vol. I, 428 (1932).

(11) Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945).

(12) Adams and Whitmore, *ibid.*, **67**, 736 (1945).

steam-bath for eighteen hours. After adding water, the non-aqueous layer was separated, combined with the ether extracts of the water washings, dried and distilled. The forerun consisted of an almost theoretical recovery of the excess hexamethylene dibromide, b. p. 112–114° at 12 mm. The bromoester boiled at 204–205° at 4 mm., $n^{24}D$ 1.5283. It weighed 126 g., an 82% yield.

Anal. Calcd. for $C_{13}H_{27}O_2Br$: Br, 21.76. Found: Br, 21.57.

ω-Morpholinohexyl 1-Phenylcyclohexanecarboxylate.—To 123.5 g. (0.34 mole) of the foregoing bromoester in 200 cc. of dry benzene, 59.0 g. (0.68 mole) of morpholine was added slowly. The reaction mixture was then stirred and refluxed five and one-half hours, after which the benzene layer was washed with water then extracted with acid. The base which was regenerated by the addition of alkali was extracted with ether and dried. Removal of the solvent, followed by distillation of the residue, gave 108 g. (86%) of the aminoester, b. p. 228–230° at 4 mm., $n^{24}D$ 1.5166.

By method Ia, an 87% yield of this base was obtained.

The hydrochloride melted at 121–122° after crystallization from ethyl acetate.

γ-Bromopropyl 1-Phenylcyclopropanecarboxylate.—A solution of 25 g. (0.138 mole) of 1-phenylcyclopropanecarboxylic acid chloride in 20.5 g. (0.148 mole) of trimethylene bromohydrin was heated on the steam-bath overnight. The reaction mixture was washed successively with water and sodium bicarbonate, then dried and distilled. The main fraction weighed 25.2 g., (65%) and boiled at 151–153° at 3 mm., $n^{26}D$ 1.5364.

Anal.[13] Calcd. for $C_{13}H_{15}O_2Br$: C, 55.12; H, 5.34. Found: C, 55.96; H, 5.42.

γ-Morpholinopropyl 1-Phenylcyclopropanecarboxylate.—The foregoing bromide, 11.3 g. (0.041 mole), was converted to the morpholino derivative as described above for the ω-morpholinohexyl ester. The product boiled at 173–175° at 2 mm., $n^{26}D$ 1.5193. The yield was 8.5 g. or 73%.

The hydrochloride, m. p. 168–169°, was crystallized from absolute alcohol.

Acknowledgment.—The author is indebted to Mr. E. F. Shelberg and Mr. L. F. Reed of the Microanalytical Department of these laboratories for the microanalyses and to Mr. Wm. B. Brownell for his assistance in preparing some of the intermediates.

Summary

A series of basic esters derived from 1-phenylcyclopropanecarboxylic acid and 1-phenylcyclohexanecarboxylic acid has been described.

Preliminary pharmacological data indicate that several of these esters possess pronounced antispasmodic properties.

(13) Fractionation of this material did not improve the analysis.

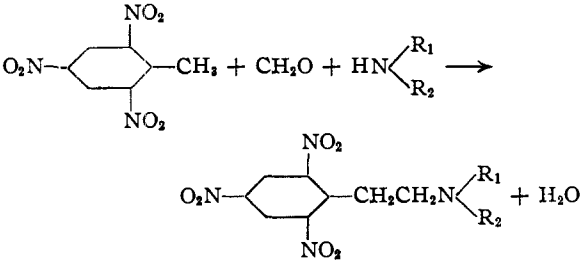
NORTH CHICAGO, ILLINOIS RECEIVED JULY 13, 1946

[CONTRIBUTION FROM ROHM AND HAAS CO., INC.]

Trinitro-phenylethyl Amines from TNT[1]

BY HERMAN A. BRUSON AND GEORGE B. BUTLER

While attempting to utilize 2,4,6-trinitrotoluene in the preparation of combustible plastics,[1a] it was found that this compound would undergo the Mannich reaction with formaldehyde and secondary amines to give 2,4,6-trinitrophenylethyl amines according to the reaction



Vender[2] prepared 2,4,5-trinitrophenylethanol by treating 2,4,5-trinitrotoluene with aqueous formaldehyde in the presence of potassium carbonate, but described no Mannich-type bases. McLeod and Robinson[3] described the formation of 2,4-dinitrophenylethyl-N-diethylamine as a yellow oil from the reaction of equivalent weights of 2,4-dinitrotoluene and the *i*-amyl ether of methylol diethylamine in boiling *i*-amyl alcohol, but could isolate no definite compounds from the reaction of these amine ethers with 2,4,6-trinitrotoluene.

Kermack and Muir[4] obtained 2,4-dinitrophenylethyl-N-diethylamine by treating equivalent quantities of 2,4-dinitrotoluene, diethylamine, and formaldehyde in boiling ethanol. They also described the formation of 1,3-dipiperidino-2-(2,4-dinitrophenyl)-propane[5] by the reaction of one mole of 2,4-dinitrotoluene with two moles each of piperidine and formaldehyde.

It also has been reported that the alkaloid berberine[6] condenses with TNT to give an orange red compound but its properties are not described. Berberine in its pseudo-base form contains an >N—CHOH— grouping, but whether this combines with TNT by loss of water or by the formation of a simple addition product is not clear.

The condensation of TNT with formaldehyde and secondary amines takes place readily at temperatures from about 0 to 100°, depending upon the amine, by mixing together equivalent weights of the reactants. In the cases of the lower, more reactive amines, low temperatures are suitable to complete the reaction, but in the cases of

(1) This paper is based on work done for the Office of Scientific Research and Development under OSRD Contract No. OEM sr-643 with the Rohm and Haas Co.

(1a) Bruson and Butler, U. S. Patent 2,400,806 (1946).

(2) Vender, *Gazz. chim. ital.*, **45**, II, 97 (1915).

(3) McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

(4) Kermack and Muir, *J. Chem. Soc.*, 300 (1933).

(5) Mannich and Stein, *Ber.*, **58**, 2659 (1925).

(6) Robinson and Robinson, *J. Chem. Soc.*, **111**, 958 (1917).