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POTENTIAL ANALGESICS AND ANTISPASMODICS. I. THE SYNTHESIS OF OPEN-CHAIN ANALOGS OF DEMEROL[1]

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Some interest has been evidenced in open-chain analogs of the successful analgesic Demerol (1). Our work was directed toward the preparation of several α-phenyl-α-ethyl-γ-substituted butyronitriles and butyrates. Varying analgesic and anticonvulsant activity has been reported for a number of *gamma*-amino compounds of this class (2) but little work has been done on the *alpha*-ethyl compounds.

In our work α-phenylbutyronitrile, starting compound for the syntheses, was prepared by a modification of the procedure of Bodroux and Taboury (3) employing the alkylation of phenylacetonitrile with ethyl iodide in the presence of powdered sodium amide, with yields of 62–84%. Some doubt has been cast on the purity of previous samples of this nitrile (4) and so a careful separation of product from starting material and disubstituted phenylacetonitrile was effected. The α-phenylbutyronitrile was treated with ethylene chloride in the presence of sodium amide to give α-phenyl-α-ethyl-γ-chlorobutyronitrile by a modification of the procedure of Murray and Cloke. This chloro compound was then treated with benzylmethylamine, piperidine, and diethylamine to provide quantities of the corresponding *gamma*-amino nitriles. Some advantage of this method for preparing the *gamma*-amino nitriles may be claimed over the conventional method using a sodium amide-induced condensation of the unstable *beta*-chloro amine with the phenylacetonitrile. A disadvantage is that sealed tubes or autoclaves are required for the more volatile amines. The chloro compound can be prepared in about 50% yield from α-phenylbutyronitrile. It is quite stable, depositing a solid material only very slowly on standing. Yields of the *gamma*-amino nitriles from the chloro compound were 41–82%. Samples of the *gamma*-diethylamino and *gamma*-benzylmethylamino butyronitriles were also prepared by the usual condensation reaction, employing the *beta*-chloroamine. Likewise α-phenyl-α-ethyl-γ-dimethylamino butyronitrile was prepared this way. α-Phenyl-α-ethyl-γ-phenoxy butyronitrile, a possible intermediate in further work, was made from α-phenylbutyronitrile and β-bromoethyl phenyl ether. Yields and properties of the nitriles are recorded in Table I.

Undoubtedly some reaction of ethylene chloride with two moles of α-phenylbutyronitrile takes place, to give a cross-linking, but none of this product could

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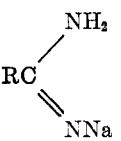
TABLE I

YIELDS AND PHYSICAL PROPERTIES OF NITRILES, $C_6H_5CR(C_2H_5)CN$

R	YIELD, %	B.P., °C.	MM.	n_D^{25}	d_4^{25}	M_R[a] Calc'd	M_R Found	ANALYSES							
								C		H		N		X	
								Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
H[c]	62–84	89.0–89.5	3.2	1.5058	0.9665	44.51	44.62	82.71	82.57[b]	7.64	7.58[b]				
$(CH_2)_2Cl$[d]	50	110–112	2.0	1.5211	1.0784	58.61	58.66							17.07	17.07[b]
$(CH_2)_2Br$	6	119–120	1.0	1.5377	1.2753	61.51	61.82	57.15	57.37[e]	5.60	5.56[e]	5.56	5.66[e]	31.69	31.55[e]
$(CH_2)_2OC_6H_5$	56	195	2.0	1.5506	1.0609	79.49	79.71	81.52	81.39[b]	7.22	7.21[b]				
$(CH_2)_2N(CH_3)_2$[f]	61[m]	131–133	4.0					Analyzed as ester hydrochloride							
$(CH_2)_2N(C_2H_5)_2$[g, h]	53[m]	140–143	4.0	1.5004	0.945	76.16	76.1					11.47	11.37[b]		
	41[n]														
$(CH_2)_2N(CH_3)CH_2C_6H_5$[i]	48[m]	176–180	2.0	1.5422	1.0136	91.03	90.90	82.06	82.17[b]	8.26	8.39[b]	9.57	9.59[b]		
	77[n]														
$(CH_2)_2NC_5H_{10}$[k, l]	80[n]	150–154	1.5	1.5190				Analyzed as ester hydrochloride							

[a] Calculated from the values of von Auwers and Eisenlohr given in Gilman's *Organic Chemistry* (12) except for the nitrile group for which von Auwer's value of 5.446 for that in *n*-butyronitrile was used (13). [b] Microanalyses by Oakwold Laboratories, Fairfax, Virginia. [c] Baldinger and Nieuwland (14) reported n_D^{25} 1.5077, d_4^{25} 0.9717. [d] Hastings and Cloke (15) gave n_D^{20} 1.5225, d_4^{20} 1.0784. [e] Microanalysis by Galbraith Laboratories, Knoxville, Tenn. [f] M.p. of hydrochloride 193–195°. [g] M.p. of hydrochloride 172–173°. [h] Bergel and coworkers (16) reported b.p. 161–166° (10–12 mm.). [i] M.p. of hydrochloride 161–162°. [k] M.p. of hydrochloride 219–220°. [l] NC_5H_{10} is N-piperidine. [m] Made by condensation of α-phenylbutyronitrile with the appropriate β-chloroethylamine. [n] Made by reaction of the appropriate amine with α-phenyl-α-ethyl-γ-chlorobutyronitrile.

be isolated. However, there was obtained from the reaction mixture a quantity of solid substance, which was found to be α-phenylbutyramidine hydrochloride. This was a discovery which seems to shed some light on the nature of the alkylation reaction with α,β-dihalides at least. Ziegler and Ohlinger (5) reported that treatment of a nitrile with at least one *alpha* hydrogen with alkyl halide and sodium amide could lead to alkylation or to the formation of the sodium salt of an amidine,



Others have intimated, however, that nitriles with activated *alpha*-hydrogens, as in phenylacetonitrile, would undergo dimerization rather than suffer addition of sodium amide to form the amidine derivative (6). In this connection, though, Rising and Swartz (7) found that α-phenylbutyronitrile did not undergo the dimerization (Thorpe reaction) in the presence of sodium ethoxide. Sperba, Papa, and Schwenk thought they obtained tributylacetamidine in the treatment of a mixture of capronitrile and *n*-butyl bromide with sodium amide but did not identify it (8), while Newberry and Webster obtained an almost theoretical yield of the sodium salt of the amidine from α-ethylcapronitrile and sodium amide (9).

We tried to make α-phenyl-α-ethyl-γ-bromobutyronitrile by a method like that used for the *gamma*-chloro compound but could obtain only very small yields. There was, however, much of the solid by-product, which had properties similar to that from the *gamma*-chloro compound preparation but which was a hydrobromide. Since sodium amide does not react with ethylene bromide under the conditions of the experiment, it would seem that the sodio derivative of α-phenylbutyronitrile,[5] or sodio-amidino derivative, if that be the structure, withdrew hydrogen halide from the ethylene halide, forming the amidine salt, with precipitation of sodium halide. It should be noted that, in our work, most of the alkylations resulted in a brief but vigorous evolution of ammonia upon the addition of the halide to the supposed sodium salt of the nitrile. This observation would tend to support the hypothesis of the formation of the sodio derivative of the amidine as an intermediate, ammonia being liberated from the mixture as alkyl halide is added and C-alkylation takes place. Possibly there is some competing N-alkylation (9). Other workers have reported strong evolution of ammonia upon the addition of the organic halide (3). The addition of diethyl sulfate to the sodium salt has also been shown to liberate ammonia (11).

Hydrolysis of the *gamma*-amino nitriles to the corresponding amino acids was effected with 40% sulfuric acid in an autoclave at 160–170° for about seven hours. The acids were then recrystallized and esterified with absolute ethanol and dry hydrogen chloride. Properties and yields of the acids and esters are recorded in Table II.

[5] Some workers have maintained that the sodium salt of phenylacetonitrile exists entirely in the nitride form, $C_6H_5CH{=}C{=}NNa$ (10).

TABLE II

YIELDS AND PHYSICAL PROPERTIES OF ACIDS AND ESTERS, $C_6H_5C(C_2H_5)(CH_2CH_2R)COOR'$

R'	R	YIELD, %	M.P. OR B.P., °C.	MM.	n_D^{25}	d_4^{25}	MR_D Calc'd	MR_D Found	ANALYSES					
									C		H		Cl	
									Calc'd	Found	Calc'd	Found	Calc'd	Found
H	NC_5H_{10}[e]	83[c]	243–244[k]						74.14	73.59[b]	9.15	8.78[b]		
H	$N(CH_3)_2$	85[c]	185–186[k]						Analyzed as ester hydrochloride					
H	$N(C_2H_5)_2$	80[c]	177–179[k]						73.11	73.08[b]	9.52	9.08[b]		
C_2H_5	NC_5H_{10}[e, f]	55[d]	177–811	5.0	1.5108	1.0113	89.74	89.84					10.43[i]	10.40[i]
C_2H_5	$N(CH_3)_2$[g]	20[d]	139–144	4.0	1.4962	0.9870	78.09	77.94					11.83[i]	11.85[i]
C_2H_5	$N(C_2H_5)_2$[h]	41[d]	145–149	3.0	1.4938	.9735	87.32	87.11					10.81[i]	10.54[i]

[a] Calculated from the values given in Gilman's *Organic Chemistry* (12). [b] Microanalyses by Oakwold Laboratories, Fairfax, Virginia. [c] From the nitrile. [d] From the acid. [e] NC_5H_{10} is N-piperidino. [f] M.p. of hydrochloride 129–130°. [g] M.p. of hydrochloride 133–134°. [h] M.p. of hydrochloride 103–104°. [i] As the hydrochloride. [k] M.p.

Pharmacological screening tests were carried out on ethyl α-phenyl-α-ethyl-γ-dimethylaminobutyrate hydrochloride, ethyl α-phenyl-α-ethyl-γ-diethylaminobutyrate hydrochloride and ethyl α-phenyl-α-ethyl-γ-piperidylbutyrate hydrochloride.[6] As antispasmodics these compounds showed a 1+ activity on the isolated intestinal strip from a rabbit indicating a weak tendency to lessen the tone of smooth muscle. No analgetic activity was detected when these compounds were tested at their maximum tolerated doses in a mouse electrical test.

EXPERIMENTAL

α-Phenylbutyronitrile. This compound was prepared by a modification of the procedure of Bodroux and Taboury. The best procedure was as follows: Eastman redistilled benzyl cyanide, 235 g. (2.00 moles) was added over a period of four hours to a stirred suspension of 86.0 g. (2.20 moles) of sodium amide in a 2-liter, 3-necked flask equipped with a dropping-funnel, mercury-sealed Hirschberg stirrer, and condenser protected with a soda-lime drying tube from which an outlet tube led to an ammonia absorption trap. The mixture was then refluxed two hours, whereupon 312 g. (2.00 moles) of ethyl iodide was added over a period of four hours, followed by an additional two hours of refluxing. After the final refluxing a sufficient quantity of water was added to dissolve all the solid material, the layers were separated, and the water layer was extracted several times with small portions of ether. The extracts and the ether layer were combined, washed, and dried over magnesium sulfate. After drying, the ether was removed on a water-bath under an aspirator and the product was distilled through a 27-cm. Vigreux column at a pressure of 25 mm. The main portion distilled at 130.2–133.2°. Redistillation of the later fraction gave a total yield of 483 g. or 81%. There was only a slight loss on redistillation at 89.3° (3.2 mm.). The redistilled product was used for analysis and the determination of physical constants. The higher pressure was used for the first distillation as preliminary work showed that separation of the benzyl cyanide and dialkylated compound, especially the former, was more efficient there.

α-Phenyl-α-ethyl-γ-chlorobutyronitrile. When the procedure of Murray and Cloke was employed directly, using 1.74 moles of α-phenylbutyronitrile, a considerable quantity of crystalline solid separated (9.2 g. when dry), which appeared to be α-phenylbutyramidine hydrochloride (*cf.* preparation of the *gamma*-bromo nitrile). This was filtered off and the filtrate was distilled, giving 176 g. of the desired product. Redistillation at about 100° (0.5 mm.) gave 158 g. of chloro compound, but distillation was difficult. The most satisfactory procedure found for preparing this compound was the following one. Using the same apparatus that was employed in the preparation of α-phenylbutyronitrile, 40.0 g. (1.02 moles) of sodium amide suspended in one liter of dry benzene was treated with 145.2 g. (1.00 mole) of α-phenylbutyronitrile over a 1.5 hour period while the reaction flask was held in an ice-bath. Following the addition of the nitrile the mixture was allowed to warm up to 40°, was then cooled to −10° and 200 g. (2.03 moles) of ethylene chloride was added quickly (15 min.). A vigorous reaction ensued, accompanied by an evolution of ammonia and a rapid thickening and darkening of the reaction mass. When the reaction had subsided, the mixture was refluxed for 14 hours (with alternate periods of standing so that the total contact time was 24 hours). Water was then added and the layers were separated. The benzene layer was washed once with water and the water layer was extracted twice with benzene. The benzene solution was dried over calcium chloride and distilled. No solid separated as the benzene and excess ethylene chloride were taken off under reduced pres-

[6] The authors wish to thank Dr. J. H. Williams, Director of Chemical Research and Dr. R. W. Cunningham, Department of Pharmacology, Lederle Laboratories Division, American Cyanamid Company for the pharmacological tests.

sure. Two easy distillations of the liquid remaining gave 62.1 g. (0.43 mole) of recovered α-phenylbutyronitrile and 105.4 g. (0.51 mole) of α-phenyl-α-ethyl-γ-chlorobutyronitrile boiling at 110–112° (2.0 mm.). This represented a 50.8% yield of product based on the starting quantity of α-phenylbutyronitrile.

Other procedures, using not as cold a flask for the addition of ethylene chloride and/or not as long a period of refluxing following that addition, gave some of the previously mentioned solid by-product. When a special apparatus was used in which a warm toluene solution of the sodio derivative of α-phenylbutyronitrile was added to an excess of ethylene chloride, only a trace of the *gamma*-chloro compound was formed, the chief product being the amidine hydrochloride.

Tests on the solid by-product. This material was recrystallized from absolute ethanol, giving a white crystalline substance, m.p. 282–283°, with charring beginning at 265°.

Anal. Calc'd for $C_{10}H_{14}N_2 \cdot HCl$: C, 60.44; H, 7.61; N, 14.10; Cl, 17.85.

Found:[7] C, 60.50; H, 7.79; N, 14.05; Cl, 17.63.

This substance was hydrolyzed by boiling with dilute sodium hydroxide solution to give a good yield of α-phenylbutyramide, m.p. 84–85° (recrystallized from ligroin) and a trace of α-phenylbutyric acid, m.p. 39–41°. Neither of these two products showed any depression of the melting point when mixed with Eastman Kodak samples. A picrate was prepared by warming an alcoholic solution of the salt with picric acid, yellow needles m.p. 220–226°d. This picrate showed no depression of the melting point when it was mixed with a picrate prepared similarly from the solid by-product from the α-phenyl-α-ethyl-γ-bromobutyronitrile preparation.

α-Phenyl-α-ethyl-γ-bromobutyronitrile. Three procedures for the reaction of α-phenylbutyronitrile with ethylene bromide were tried in attempts to prepare a reasonable quantity of this compound. One was suggested by the work of Eisleb and involved the treatment at 100° of a benzene solution of α-phenylbutyronitrile and three times the molecular quantity of ethylene bromide with powdered sodium amide. Although there appeared to be a reaction, no bromide was obtained (89% recovery of α-phenylbutyronitrile). The second method made use of the special apparatus whereby the sodio derivative of the nitrile could be added to an excess of ethylene bromide. A 4.3% yield of product was obtained on second distillation. The third procedure, an adaptation of that of Murray and Cloke for the *gamma*-chloro compound gave a 6.2% yield of product on second distillation. In all three of the preparations some of the solid by-product was obtained (especially in the second and third procedures). Since much sodium bromide was formed also in the second and third preparations, it would appear that hydrogen bromide was withdrawn from the ethylene bromide. The solid by-product was recrystallized from an alcohol-ether mixture to give white needles, m.p. 237.5–238.5° with slight decomposition. Analysis and tests similar to those on the by-product from the γ-chloro compound preparation indicated it to be slightly impure α-phenylbutyramidine hydrobromide.

α-Phenyl-α-ethyl-γ-phenoxybutyronitrile. This compound was prepared using a reported procedure for α-phenyl-γ-phenoxyvaleronitrile (17). After removal of the ether from the dried solution the residue was distilled. A forerun of α-phenylbutyronitrile represented a recovery of 35%. Distillation of the product through a 27-cm. Vigreux column at 191–196° (2.0 mm.) gave a 56% yield based on the starting nitrile. A portion was redistilled for analysis and the determination of physical constants. The compound when freshly distilled was a pale amber, viscous oil. A small amount of waxy, white solid separated from this oil on standing.

Treatment of α-phenyl-α-ethyl-γ-chlorobutyronitrile with secondary amines. This reaction proceeds quite readily in the presence of a hydrogen chloride acceptor and at elevated temperatures. An excess of amine usually serves as the hydrogen chloride acceptor. In some cases it was advisable to add an inert solvent or a considerable excess of amine to keep the reaction mixture liquid. The reaction rate can be followed easily from the amount

[7] Analysis by Galbraith Laboratories, P. O. Box 32, Knoxville, Tennessee.

of insoluble amine hydrochloride formed. In the condensation with piperidine, heating at the reflux temperature proved satisfactory. When benzylmethylamine was used, a temperature sufficiently high to liquefy the benzylmethylamine hydrochloride formed was employed. For diethylamine it was necessary to use a sealed tube or autoclave.

α-Phenyl-α-ethyl-γ-benzylmethylaminobutyronitrile. Benzylmethylamine, 45.0 g. (0.372 mole), and α-phenyl-α-ethyl-γ-chlorobutyronitrile, 38.6 g. (0.186 mole), were heated at 200–211° for eight hours in a round-bottomed flask fitted with a reflux condenser and drying tube. After cooling, the mixture was treated with dilute hydrochloric acid to dissolve all the basic material and the unreacted chloro compound was extracted with ether. (This compound can be recovered by drying and distilling the extract.) After the aqueous solution was made alkaline with potassium hydroxide, the amines were extracted with three portions of ether, the combined extracts were dried over potassium carbonate, and then the ether was removed under an aspirator. Careful fractionation of the residue gave 41.7 g. or 77% yield of the anticipated amine. This aminonitrile was shown to be identical with that prepared from the condensation of α-phenylbutyronitrile with β-chloroethyl benzylmethylamine (b.p., n_D^{25}, m.p. of hydrochloride).

α-Phenyl-α-ethyl-γ-diethylaminobutyronitrile. The chloronitrile, 12.77 g. (0.614 mole) and diethylamine, 23.36 g. (0.246 mole), were sealed in a glass tube and heated in an oil-bath at 130° for 15 hours. When the product was worked up as for the *gamma*-benzylmethylamino compound, 6.2 g. of the desired amine was obtained (41% yield). There was a 41% recovery of the starting chloronitrile.

CONDENSATION OF α-PHENYLBUTYRONITRILE WITH *beta*-CHLOROAMINES

(*a*) *With β-chloroethylbenzylmethylamine.*[8] The procedure of Bergel and co-workers (18) for the preparation of α-phenyl-γ-benzylmethylaminobutyronitrile was followed, using equimolar quantities of reactants. There was obtained 23 g. of α-phenyl-α-ethyl-γ-benzylmethylaminobutyronitrile from 23.7 g. of α-phenylbutyronitrile (48% yield). The hydrochloride of this and the other aminonitriles was made by treating an ether solution of the aminonitrile with dry hydrogen chloride and recrystallizing the salt from an alcohol-ether mixture.

(*b*) *With β-chloroethyldiethylamine.* Using the procedure of Bergel and co-workers (16), a 56% yield of the desired aminonitrile was obtained. In another experiment using a modification of the procedure of Newman and Closson (19) a 53% yield of product was obtained when α-phenylbutyronitrile was added to a stirred suspension of sodium amide in toluene at 0°, followed by an hour of heating on a steam-bath, and then the addition of an ether solution of β-chloroethyldiethylamine to the sodio derivative kept in an ice-salt bath. The mixture was allowed to warm to room temperature over a period of several hours and then was refluxed on a water bath for six hours.

(*c*) *With β-chloroethyldimethylamine.* Following a procedure given in the "Kleiderer Report" for the preparation of the nitrile intermediate in the synthesis of amidone (20), 72.5 g. (0.50 mole) of α-phenylbutyronitrile and 53.7 g. (0.50 mole) of β-chloroethyldimethylamine were caused to react using 20.0 g. (0.50 mole) of sodium amide. During the final refluxing period the yellow-orange mixture suddenly became very viscous and then gradually thinned. After the mixture was cooled, water was added to dissolve the sodium chloride and the benzene layer was removed and extracted five times with 50-ml. portions of 2 *N* hydrochloric acid. After washing the combined acid extracts twice with ether, the solution was made strongly alkaline with potassium hydroxide. The yellow oil which formed was taken up in ether, dried over potassium carbonate, and distilled. After removal of the ether and on careful fractionation, 65.5 g. of colorless product was obtained, b.p 131–133° (4.0 mm.) (61% yield). Some α-phenylbutyronitrile was recovered from the original benzene layer and the ether washings of the acid solution, 12.3 g. (17%).

[8] Prepared by the reaction of benzylmethylamine with ethylene chlorobromide in ether at 40–45° for 18 hours.

Preparation of the gamma-aminobutyric acids. A typical procedure, for α-phenyl-α-ethyl-γ-piperidylbutyric acid, is as follows: 29 g. (0.108 mole) of the piperidyl butyronitrile was dissolved in 100 g. of 40% sulfuric acid and heated at 160–170° for seven hours in an autoclave at about 100 p.s.i. Then the mixture was made alkaline and extracted with ether to recover unhydrolyzed nitrile (2.8 g.). The alkaline solution was neutralized with sulfuric acid, the mixture was evaporated to dryness on a steam-bath, and then was extracted with hot absolute ethanol. On concentration of the alcoholic solution and after two recrystallizations from the minimum amount of water, 24.8 g. (83% yield) of the amino acid was obtained, m.p. 236–238° which upon further recrystallizations was raised to 243–244°.

Preparation of the ethyl gamma-aminobutyrates. A typical procedure, for ethyl α-phenyl-α-ethyl-γ-piperidyl butyrate, is as follows: The piperidylbutyric acid, 6.2 g. (0.022 mole) was dissolved in 350 ml. of absolute ethanol. Dry hydrogen chloride was passed through this solution for eight hours after which the major portion of the alcohol was distilled off as hydrogen chloride was still passed in. The residue was poured into a mixture of ice and water and made alkaline with cold sodium hydroxide solution. The oil which formed was taken up in ether and the aqueous solution was extracted three times with ether. The ether solution and the extracts were combined and dried over magnesium sulfate. Distillation gave 3.8 g. (56% yield) of ester boiling at 161–164° (2.0 mm.). A sample of the ester dissolved in ether and treated with hydrogen chloride gave a precipitate of hydrochloride, white platelets, m.p. 129–130°.

SUMMARY

A new method of synthesis of open-chain analogs of Demerol has been employed, in which secondary amines are condensed with α-phenyl-α-ethyl-γ-chlorobutyronitrile. This method of preparation is compared with the condensation of *beta*-chloroethylamines with α-phenylbutyronitrile which was used also. Several new α-phenyl-α-ethyl-γ-substituted butyronitriles were prepared and three new α-phenyl-α-ethyl-γ-amino butyrates have been prepared from the corresponding acids which were obtained from the nitriles by hydrolysis. In the preparation of α-phenyl-α-ethyl-γ-chlorobutyronitrile, α-phenylbutyramidine hydrochloride was isolated. A corresponding salt was isolated in considerable quantity from the preparation of α-phenyl-α-ethyl-γ-bromobutyronitrile. The formation of this by-product is discussed. The three new butyrates were tested pharmacologically and found to have weak antispasmodic and no analgetic activity.

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LITERATURE REFERENCES

(1) EISLEB, *Ber.*, **74**, 1433 (1941); BLICKE AND CHANIN, Abstracts of Papers, 109th meeting American Chemical Society, Atlantic City, April 8–12, 1946, p. 54K.
(2) BLICKE AND CHANIN, Ref. (1); BILLMAN, SMITH, AND RENDALL, *J. Am. Chem. Soc.*, **69**, 2058 (1947).
(3) BODROUX AND TABOURY, *Bull. soc. chim.*, [4] **7**, 666 (1910).
(4) RISING, *J. Am. Chem. Soc.*, **42**, 128 (1920); MURRAY AND CLOKE, *J. Am. Chem. Soc.*, **68**, 126 (1946).
(5) ZIEGLER AND OHLINGER, *Ann.*, **495**, 84 (1932).
(6) SHRINER AND NEUMANN, *Chem. Revs.*, **35**, 351 (1944).
(7) RISING AND SWARTZ, *J. Am. Chem. Soc.*, **54**, 2020 (1932).
(8) SPERBA, PAPA, AND SCHWENK, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

(9) NEWBERRY AND WEBSTER, *J. Chem. Soc.*, 738 (1947).
(10) UPSON, MAXWELL, AND PARMELEE, *J. Am. Chem. Soc.*, **52,** 1971 (1930).
(11) BOWDEN, *J. Am. Chem. Soc.*, **60,** 131 (1938).
(12) GILMAN, *Organic Chemistry,* Vol. II, 2nd ed., John Wiley and Sons, New York, 1943, p. 1751.
(13) VON AUWERS, *Ber.*, **60,** 2122 (1927).
(14) BALDINGER AND NIEUWLAND, *J. Am. Chem. Soc.*, **55,** 2851 (1933).
(15) HASTINGS AND CLOKE, *J. Am. Chem. Soc.*, **56,** 2136 (1934).
(16) BERGEL, HAWORTH, MORRISON, AND RINDERKNECHT, *J. Chem. Soc.*, 261 (1944).
(17) WALTERS AND MCELVAIN, *J. Am. Chem. Soc.*, **55,** 4625 (1933).
(18) BERGEL, HINDLEY, MORRISON, AND RINDERKNECHT, *J. Chem. Soc.*, 269 (1944).
(19) NEWMAN AND CLOSSON, *J. Am. Chem. Soc.*, **66,** 1553 (1944).
(20) Office of the Publication Board, U. S. Dept. of Commerce, Report No. PB-981, p. 97.