Summary

We have studied the polymerization of ketene in the gaseous and liquid phases and in solution.

Ketene does not appear to polymerize appreciably in the gas phase at room temperature. Polymerization only sets in at one or more points on the surface of the vessel after the gaseous ketene has stood for several hours.

The pure liquid is stable at −80° but at 0° polymerization is rapid and is complete in about one and one-half hours.

In solution, ketene polymerizes according to a bimolecular law; within the limits of our experimental error (±20%) antioxidants such as hydroquinone do not inhibit the reaction and peroxides such as ascaridole or acetone peroxide do not accelerate it. There is a wide variation in the rate of polymerization depending on the solvent used and there seems to exist a rough parallelism between the rate and the dielectric constant of the solvent; solvents of high dielectric constant favor polymerization. The activation energy of the polymerization process in acetone is 11,000 cal.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF VERMONT]

The Preparation of Some Monoguanidines of Possible Physiological Significance[1]

BY CHARLES E. BRAUN AND WINIFRED M. RANDALL

Physiological studies in this Laboratory have shown that, when administered subcutaneously to normal rabbits, benzylguanidine produces a hyperglycemia followed by a marked hypoglycemia, and that β-phenylethylguanidine also exerts a hypoglycemic effect but with a less marked preliminary hyperglycemia. The latter compound, in larger doses, exerts a powerful effect upon the flow of blood as evidenced by the difficulty of bleeding the animals. The physiological effects of these compounds, together with their apparent low toxicity and the fact that they produced no observed deleterious effects upon the dosed animals, suggested the extension of these types for use in studying the relationship between guanidine structure and hypoglycemic activity.

With this in mind, the following series of new monoguanidines was prepared: γ-phenylpropylguanidine sulfate, ϑ-phenylbutylguanidine sulfate, hexahydrobenzylguanidine sulfate, β-cyclohexylethylguanidine sulfate, α,α-phenylbenzylguanidine hydrochloride, α,α-dibenzylguanidine hydrochloride, α,β,γ-tribenzylguanidine trihydrochloride and α,β,γ-tribenzylguanidine monohydrochloride.

α,γ-Dibenzylguanidine hydrochloride was synthesized by a new method involving S-methyl benzylisothiourea hydroiodide not previously described in the literature. The hydrochloride melted at 186°, which is not in agreement with 176° as reported by Strakosch who prepared it from benzylcyanamide and benzylamine hydrochloride.[2]

The reactions involved in our synthesis of α,γ-dibenzylguanidine hydrochloride establish definitely that the two benzyl radicals must be on the α and γ nitrogen atoms. This, plus the analytical data and the fact that our compound had the same characteristics, including slight water solubility ascribed by Strakosch to his compound, argues that the two are identical, and that the previously reported melting point is in error. Strakosch's compound was impure as shown by the fact that the chlorine content was low, 11.42% as compared to the calculated value of 12.86% and not 11.07% as recorded in his paper.

Experimental

S-Methyl isothiourea sulfate, m. p. 245°, was obtained as described by Arndt.[3]

γ-Phenylpropylamine, b. p. 121–124° (30–35 mm.), was prepared from β-phenylethyl bromide (Eastman) by converting it into the cyanide and reducing the latter with sodium and absolute alcohol.

ϑ-Phenylbutylamine, b. p. 142–144° (42 mm.), was obtained by converting γ-phenylpropyl alcohol into its bromide according to the method of Norris, Watt and Thomas,[4] transforming the bromide into the cyanide, and reducing the latter as described above.

(1) Abstracted from a thesis submitted by Winifred M. Randall in partial fulfilment of the requirements for the degree of Master of Science in the Graduate School of the University of Vermont.

(2) J. Strakosch, *Ber.*, **5**, 695 (1872).

(3) F. Arndt, *ibid.*, **54**, 2236 (1921).

(4) J. Norris, M. Watt and R. Thomas, THIS JOURNAL, **38**, 1071 (1916).

TABLE I

EXPERIMENTAL DATA ON PREPARATION AND PROPERTIES OF MONOGUANIDINE SALTS

Abbreviations: alc, alcohol; eth, ether; aq, water; ac, acetone; s, soluble; sls, slightly soluble; vs, very soluble; i, insoluble; h, hot; c, cold; S-methyl, S-methyl isothiourea sulfate; ost, outside temperature; aq B, water-bath; w B, wax bath; rfx, reflux; D, decomposes.

No.	Reactants Name	G.	Reaction conditions Med.	Vol., cc.	Temp., °C.	Time, hrs.	Reaction product Name
1	γ-Phenylpropylamine	10.16	alc	51	rfx	1.5	γ-Phenylpropylguanidine sulfate[a]
	S-methyl	10.50			aq B		
2	ϑ-Phenylbutylamine	38.00	alc	190	rfx	10	ϑ-Phenylbutylguanidine sulfate[b]
	S-methyl	35.50			aq B		
3	Hexahydrobenzylamine	2.8	alc	95	rfx	3.5	Hexahydrobenzylguanidine sulfate[c]
	S-methyl	4.4			aq B		
4	β-Cyclohexylethylamine	6.0	alc	150	rfx	26	β-Cyclohexylethylguanidine sulfate[d]
	S-methyl	6.6			aq B		
5	Phenylbenzylamine HCl	21.9	abs	250	rfx	7	α,α-Phenylbenzylguanidine hydrochloride[e]
	Cyanamide (Eastman)	6.5	alc		aq B		
6	Dibenzylamine HCl	12.0	amyl	60	140–50	4	α,α-Dibenzylguanidine hydrochloride[f]
	Cyanamide	3.0	alc		ost		
7	*Sym*-dibenzylthiourea	27.0	abs	300	rfx	60	α,β,γ-Tribenzylguanidine trihydrochloride[g]
	Benzylamine (Eastman)	11.3	alc		aq B		
	Mercuric oxide	87.0					
8	*Sym*-dibenzylthiourea	25.0	amyl	200	rfx	15	α,β,γ-Tribenzylguanidine monohydrochloride[h]
	Benzylamine	10.5	alc		w B		
	Mercuric oxide	40.0					
9	S-Methylbenzylisothiourea HI	4.25	aq	20	rfx	2	α,γ-Dibenzylguanidine hydrochloride[i]
	Benzylamine	1.48			aq B		

No.	Recryst. solvent	Solubility Aq	Alc	Abs Alc	Ac	Yield (purified) g.	%	M. p.,[j] °C.	Formula	Analyses, % Calcd.	Found
1	alc	s(h)	s(h)	i(c)		12.3	72.3	173–174	$C_{10}H_{16}N_3 \cdot 0.5H_2SO_4$	S, 7.09	7.09
2	abs alc + ac	vs(h)		vs(h)	i(c)	23.5	38.4	175–176	$C_{11}H_{17}N_3 \cdot 0.5H_2SO_4$	S, 6.67	6.69
3	alc & abs alc	s(h)	s(h)	s(h)		2.0	39.6	275–276 280–282D	$C_8H_{17}N_3 \cdot 0.5H_2SO_4$	S, 7.85	8.07
4	aq	s(h)	i(c)	i(c)		3.0	29.1	295–297	$C_9H_{19}N_3 \cdot 0.5H_2SO_4$	S, 7.34	7.21
5	abs alc + eth	s(c)	s(h)	s(h)		6.0	23.0	248.5	$C_{14}H_{16}N_3Cl$	Cl, 13.55	13.50
6	abs alc + eth	s(c)	s(h)	s(h)		6.9	48.6	191–192	$C_{15}H_{18}N_3Cl$	Cl, 12.86	12.83
7	abs alc	vs(c)	vs(h)	vs(h)		2.9	6.3[k]	258–259	$C_{22}H_{26}N_3Cl_3$	Cl, 24.25	24.20
8	abs alc + eth	sls(c)	s(h)	s(h)		7.0	19.6[k]	203–204	$C_{22}H_{24}N_3Cl$	Cl, 9.70	9.90
9	aq	sls(c)	s(h)			2.0	52.6[l]	186	$C_{15}H_{18}N_3Cl$	Cl, 12.86	12.91

[a] Crystallized from reaction solvent upon cooling. [b] Reaction solvent evaporated off; residue treated with cold acetone and dry ether. [c] Crystallized from reaction solvent after concentrating. [d] Compound obtained by complete evaporation of reaction solvent. [e] Reaction solvent was concentrated on a steam-bath; dry ether added to precipitate the guanidine salt. [f] Anhydrous ether added to precipitate the guanidine salt. [g] Solution was filtered to remove mercuric sulfide and unreacted mercuric oxide. Dry hydrogen chloride was passed into the filtrate until heat was no longer evolved, and the solution was evaporated to dryness on a steam-bath. The tribenzylguanidine trihydrochloride was obtained by extracting the residue with hot water (25 cc.). The insoluble dibenzylthiourea was heated again for forty hours with 10 g. of benzylamine and 35 g. of mercuric oxide and the alcoholic solution treated as described. [h] Reaction suspension was treated as described in *g* and ether added to the alcoholic filtrate to precipitate the monohydrochloride salt. The crude product was extracted with hot water, 20 cc., to separate the small amount of trihydrochloride salt formed in the reaction. [i] After cooling the solution, the reaction product formed as an amorphous mass; 60 cc. of hot water was added and the solution made strongly alkaline with caustic. The crystalline base which formed upon cooling was dissolved in 50 cc. of absolute alcohol and the solution made strongly acid with hydrochloric acid. Upon diluting with cold water the difficultly soluble hydrochloride salt crystallized out. [j] Melting points were determined after drying at 100° *in vacuo*. All compounds were stable, white and insoluble in anhydrous ether. [k] Based on dibenzylthiourea. [l] Based on S-methylbenzylisothiourea hydroiodide.

Hexahydrobenzylamine, b. p. 70° (25 mm.) 162–163 (756 mm.), was prepared as follows. Hexahydrobenzoic acid, b. p. 226–229°, was obtained from both cyclohexyl bromide and cyclohexyl chloride by the methods described by Gilman and Zoellner,[5] and "Organic Syntheses."[6] The acid was converted into hexahydrobenzoyl chloride,

(5) H. Gilman and E. A. Zoellner, THIS JOURNAL, **53**, 1945 (1931).
(6) "Organic Syntheses," Coll. Vol. I, 1932, p. 353.

b. p. 179–180°, with thionyl chloride as described by Fourneau, Montaigne and Puyal.[7] Hexahydrobenzamide, m. p. 183–185°, was prepared from the acid chloride and ammonia. The nitrile, b. p. 185–187°, obtained by distilling the amide with phosphorus pentoxide, upon reduction yielded hexahydrobenzylamine.

β-Cyclohexylethylamine, b. p. 80–85° (20–25 mm.), was prepared as described by Wallach[8] from cyclohexylacetic acid. Cyclohexyl bromide with the sodio derivative of malonic ester gave cyclohexylmalonic ester, b. p. 157–158° (19 mm.). Saponification of the ester yielded cyclohexylmalonic acid, m. p. 178–181° (with evolution of carbon dioxide). Decarboxylation of this acid at 200° as described by Eykman[9] gave cyclohexylacetic acid, b. p. 145–146° (28–30 mm.). This was converted into cyclohexylacetyl chloride, b. p. 195–200°, with thionyl chloride. The acid chloride and ammonia gave cyclohexylacetamide, m. p. 185–186°, which upon distillation with phosphorus pentoxide, yielded cyclohexyl acetonitrile, b. p. 200–205°. (Wallach reported a b. p. of 215–217° for this nitrile.) Reduction of the nitrile gave the amine.

Phenylbenzylamine hydrochloride, m. p. 210–212°, and dibenzylamine hydrochloride, m. p. 256–258°, were prepared by passing dry hydrogen chloride into cold ethereal solutions of the respective amines (Eastman).

Symmetrical dibenzylthiourea, m. p. 142–145°, and benzylthiourea, m. p. 155–157°, were prepared from benzylamine (Eastman) as described by Dixon.[10]

S-Methyl benzylisothiourea hydroiodide was prepared as follows: 8.0 g. (0.0481 mole) of benzylthiourea and 7.0 g. (0.0493 mole) of methyl iodide, b. p. 42–43°, in 45 cc. of absolute alcohol were heated under reflux on a water-bath for half an hour. Dry ether was added to the cooled solution to permanent turbidity. Vigorous stirring at 0° gave a crystalline precipitate which was filtered off and washed with dry ether. The crude salt, 14 g., was dissolved in 25 cc. of hot absolute alcohol, bone blacked, filtered and ether added to permanent turbidity. The crystalline precipitate which formed was filtered off, washed with dry ether and air dried. The purified S-methyl benzylisothiourea hydroiodide was white, readily soluble in cold water and alcohol but insoluble in ether. It melted at 103–104°. The yield (purified salt) was 11.5 g. or 78.2%.

Anal. Calcd. for $C_9H_{13}N_2SI$: I, 41.19. Found: I, 41.19.

The isomer of this compound, N,N'-methylbenzylthiourea, was prepared by Dixon[11] from methyl mustard oil and benzylamine. It is erroneously listed in Richter's "Lexikon" as S-methylbenzylisothiourea.

General Methods of Preparation of Guanidines.—The monoguanidines reported here were made by either of two methods: (a) from a 1° or 2° amine hydrochloride and cyanamide, or (b), from a 1° or 2° amine and S-methylisothiourea sulfate. (In the preparation of α,γ-dibenzylguanidine hydrochloride S-methylbenzylisothiourea hydroiodide was used.) The experimental details, physical constants, properties and analytical data are recorded in Table I.

The major part of this investigation was supported by a Sigma Xi Research Grant.

Summary

1. The preparation and properties of salts of seven new monoguanidines are described.

2. The preparation and properties of S-methyl benzylisothiourea hydroiodide and its application in a new synthesis of α,γ-dibenzylguanidine hydrochloride are reported.

(7) Fourneau, Montaigne and Puyal, *Anales soc. espaü. fis. quim.*, **19**, 192 (1921).

(8) O. Wallach, *Ann.*, **353**, 295 (1907).

(9) J. F. Eykman, *Chemisch Weekblad*, **6**, 701 (1909).

(10) A. E. Dixon, *J. Chem. Soc.*, **59**, 552 (1891).

(11) A. E. Dixon, *J. Chem. Soc.*, **55**, 619 (1889).

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[CONTRIBUTION FROM THE WALKER CHEMICAL LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE]

The Synthesis of Alpha-alkyl-alpha-phenyl-gamma-chlorobutyronitriles[1]

BY RANDALL HASTINGS AND JOHN B. CLOKE

The synthesis of a series of α-alkyl-α-phenyl-γ-chlorobutyronitriles, $ClCH_2CH_2C(R)(C_6H_5)CN$, was undertaken in order to supply intermediates for some work on pyrroline structure now under way in this Laboratory. The present paper is an extension of previous work by Knowles and Cloke.[2] In their work a method was described for the synthesis of α-phenyl-γ-chlorobutyronitrile by the action of thionyl chloride on α-phenyl-γ-hydroxybutyronitrile, which, in turn, was prepared by the action of ethylene chlorohydrin on sodium phenylacetonitrile.

The first step in the present work on the synthesis of our α-alkyl-α-phenyl-γ-chlorobutyronitriles was the preparation of the proper alkylphenylacetonitriles by the method of Bodroux and Taboury.[3] In this work benzyl cyanide in ether solution was treated with an equimolar

(1) This paper has been prepared from a thesis presented by Randall Hastings to the Rensselaer Polytechnic Institute in June, 1933, in partial fulfilment of the requirements for the degree of Master of Science.

(2) Knowles and Cloke, THIS JOURNAL, **54**, 2028 (1932).

(3) Bodroux and Taboury, *Bull. soc. chim.*, **7**, 666 (1910); *Compt. rend.*, **150**, 531, 1241 (1910).