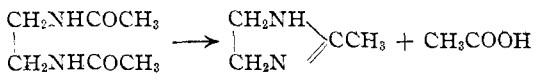
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Alkyl-glyoxalidines[1]

BY HENRY C. CHITWOOD AND E. EMMET REID

In 1875 Ladenburg[2] distilled *o*-phenylenediamine with acetic acid and obtained ethenylphenylenediamine. Hofmann[3] distilled diacetylethylenediamine in a current of hydrogen chloride and got μ-methyl-glyoxalidine.



Ladenburg[4] prepared the same compound by distilling a mixture of ethylenediamine hydrochloride with two moles of sodium acetate. The ethyl and propyl derivatives have also been made.[3,4,5]

The present investigation was undertaken to improve the method of preparation, to prepare some of the higher members of the series, and to obtain more knowledge of the physical and pharmacological properties of the alkyl-glyoxalidines.

We were unable to obtain glyoxalidine itself from diformylethylenediamine but have greatly improved the method of preparing its methyl derivative, obtaining a 68% yield as compared with 11 and 8% by following Hofmann and Ladenburg. It is a curious fact that the above reaction can be carried out by heating the diacetylethylenediamine alone or with such diverse reagents as hydrogen chloride, caustic soda, magnesia, magnesium, zinc and sodium. As acetic acid is one of the products of the reaction, the use of acid-binding materials seemed desirable. Such materials did improve the yields, magnesium giving the best.

Methyl-glyoxalidine is a strong base, melting at 105° and boiling at 198–200°. It is very soluble in water, alcohol and chloroform, less so in benzene, carbon tetrachloride and petroleum ether. It is readily brominated in cold chloroform solution, forming the hydrobromide of the monobrominated base. The bromine is probably attached to a nitrogen, since it is readily eliminated by boiling with water with the regeneration of the original base. It was hoped that it could be split off as hydrobromic acid leaving methylglyoxaline but this could not be effected. Methylglyoxalidine when heated with an aqueous alkali is hydrolyzed back to ethylenediamine. Attempts to hydrogenate or dehydrogenate it were unsuccessful. It readily forms complexes with salts of silver, copper and cobalt. When it is added to a solution of a cupric salt, copper hydroxide is precipitated and then redissolved, giving a dark blue solution. A solution of the base dissolves cobalt carbonate. It dissolves freshly precipitated silver chloride but the solution is not stable.

The alkyl-glyoxalidines, methyl to undecyl, have been prepared by heating the corresponding diacylethylenediamines with sodium or magnesium, the lower ones distilling out while the higher ones were extracted from the mass after heating. The octyl, decyl and undecyl were prepared in a molecular still. The bases were taken up in hydrochloric acid, liberated with alkali, extracted with benzene, dried over solid caustic potash and distilled *in vacuo*. The lower members of the series are hygroscopic and very soluble in water, giving strongly basic solutions. This solubility decreases with the lengthening of the alkyl side chain; the undecyl is practically insoluble in water. All dissolve in hydrochloric acid to give well-defined salts. The hydrochlorides of the three highest give soapy solutions in water. All are very soluble in alcohol and moderately so in benzene but only slightly soluble in ether or petroleum ether. The lower ones are best purified by distillation, the higher ones by recrystallization from benzene with the addition of petroleum ether. They are best identified by their picrates, which are readily formed by adding a saturated aqueous picric acid solution to solutions of the bases or of their salts. Their gold or platinum double salts are formed when the hydrochlorides of the bases are added to solutions of the metal chlorides. The gold salts were analyzed by simple ignition as recommended by Hofmann and by Klingenstein.

The necessary diacyl derivatives of ethylenediamine were prepared by heating the acids or their ethyl esters with ethylenediamine. Their solubility in water decreases rapidly as we go up

(1) From the Ph.D. dissertation of H. C. Chitwood, June, 1934.
(2) Ladenburg, *Ber.*, **8**, 677 (1875).
(3) Hofmann, *ibid.*, **21**, 2332 (1888).
(4) Ladenburg, *ibid.*, **27**, 2952 (1894).
(5) Klingenstein, *ibid.*, **28**, 1173 (1895).

the series, the diheptoyl and higher being quite insoluble. With increasing size of the alkyls they become less soluble in alcohol and more so in ethyl acetate. They are best recrystallized from mixtures of these three solvents.

The melting points of the bases, their picrates and the diacylethylenediamines from which they were prepared are given in Table I.

TABLE I

MELTING POINTS OF THE DIACYL DERIVATIVES OF ETHYLENEDIAMINE, THE ALKYLGLYOXALIDINES AND THEIR PICRATES. ANALYSES OF GOLD DOUBLE SALTS

R	Melting points, °C. $(RCONHCH_2)_2$	$RC_3H_5N_2$	Picrate	Gold salt % of gold Calcd.	Found
Methyl	175.6	105.0	205	46.49	46.55
Ethyl	191.4	38.1	137.1	45.01	45.15
Propyl	192.0	35.3	129.0	43.62	43.60
Butyl	184.2	41.0	125.8	42.30	42.38
Amyl	178.5	33.8	128.4	41.07	41.04
Hexyl	173.0	46.2	...	39.90	39.95
Heptyl	171.0	60.0	104.8	38.80	38.66
Octyl	167.0	52.1	...	37.76	38.65
Nonyl	164.6	71.4	122	36.77	36.76
Decyl	160.8	79.5	82.0	35.84	35.83
Undecyl	158.8	79.8	61.5	34.95	35.08

The picrates of the hexyl and octyl derivatives could not be made to crystallize. The melting points of the diamine derivatives show slight alteration from 5 to 11 while those of the alkyl-glyoxalidines alternate from 2 to 9 but show a reversal of the alternation at the hexyl.

Pharmacological. — Methyl - glyoxalidine, known also as lysidine, has been considered as a solvent for uric acid.[4] In friendly coöperation, the pharmacological properties of it and of the next four members of the series have been studied by Dr. David I. Macht who reports as follows.

Aqueous solutions of the compounds were tested on seedlings of *Lupinus albus*, goldfish, tadpoles, mice, rabbits and cats. Contrary to the usual pharmacological experience, the toxicity of the five compounds decreased with the increase in length of the alkyl radical. Goldfish and tadpoles survived in solutions of 1:5000 but succumbed in the order named when placed in solutions of 1:1000. Ten milligrams of the methyl compound, administered intraperitoneally, killed mice, but the higher members of the series were not so toxic. Phytotoxic indices also showed that the latter were less poisonous for plants. Half a gram per kilo of any one of these compounds, given by stomach, was not toxic for rabbits and did not impair their kidney function. The methyl compound, however, increased the acidity of the urine. Ten milligrams injected intravenously in cats under ether, produced a transient fall in blood pressure but little effect on the respiration.

Experimental

The best method of preparing methyl-glyoxalidine so far found is to heat 30 g. of diacetylethylenediamine with 5 g. of magnesium powder in a flask in a solder-bath at 270° for seventy-five minutes. The hydrogen that is evolved helps carry over the product. Some acetone was noticed. Solid potassium hydroxide is added to the distillate with boiling benzene. The reaction flask is rinsed with hot benzene. The benzene solutions are united and dried over solid caustic potash, decolorized with active charcoal, filtered and evaporated to 30 cc. On cooling the methyl-glyoxalidine crystallizes out. A second crop of crystals may be obtained by concentrating the mother liquor and adding petroleum ether; yield 12.7 g. or 68%.

In comparative experiments the yields obtained were:

Ladenburg's method	8.0%
Hofmann's method	11.4
Simple dry distillation	24.6
Distillation with sodium hydroxide	22.3
Heating with sodium	39.3
Heating with zinc	43.4
Heating with magnesium	68.0
Heating with magnesium oxide	44.0
Ethylenediamine and acetic acid	19.1
Monoacetylethylenediamine hydrochloride with sodium hydroxide	26.2

Various other methods were tried, such as distilling diacetylethylenediamine under reduced pressure or dropping it in small portions into a heated flask, but without any improvement.

The higher homologs were all prepared from the diacylethylenediamines by distilling with sodium or magnesium, or by refluxing the diamides with the metal and extracting the bases with benzene. In most cases the product was dissolved in benzene, decolorized by activated carbon, dried over potassium hydroxide and purified by vacuum distillation. When very small amounts of materials were used, as in making the octyl, decyl and undecyl glyoxalidines, the reactions were effected in a molecular still. The bases were extracted from the distillate by dilute hydrochloric acid, precipitated by addition of alkali, extracted with hot benzene and redistilled. Table II gives a summary of experiments on the production of the glyoxalidine homologs.

The diacyl derivatives of ethylenediamine as intermediates in the preparation of the bases can be made by heating ethylenediamine with the ethyl esters, although the lower members are conveniently obtained on refluxing ethylenediamine with the free acids. The solubility in water decreases abruptly in going up the series, the diheptoyl and higher derivatives being quite insoluble. They are increasingly soluble in ethyl acetate and decreasingly soluble in alcohol, and may be recrystallized from solutions in appropriate mixtures of ethyl acetate and alcohol, on cooling the solutions and on addition of one or the other of these liquids. Diformylethylenediamine closely resembles granular sugar in appearance. The diacetyl derivative crystallizes in beautiful large white prisms, while the others, due to their abrupt change in solubility on cooling, usually come down as fine light crystals.

TABLE II

PREPARATION OF ALKYL-GLYOXALIDINES

	Ethylenediamine deriv.	Wt. used	Metal	Wt.	T., °C.	Press., mm.	Time, hours	Wt. of product, g.	Yield
I	Diacetyl	30	Mg	5	270	at.	1.25	12.7	68
II	Dipropionyl	20	Mg	1.5	300	at.	5	5.2	46
III	Dibutyryl	20	Mg	1.2	330	at.	1.25	5.5	49
IV	Divaleryl	10	Mg	0.5	290	125	2.5	1.5	27
V	Dicaproyl	4	Mg	.2	190	75	1.75	0.7	34
VI	Diheptoyl	12	Mg	.5	300	at.	7	.1	1.7
VII	Dicaprylyl	1.7	Na	.1	270	at.	1	.4	47
VIII	Dipelargonyl	0.7	Na	.2	250	2	..	.08	21
IX	Dicapryl	5.5	Mg	.5	300	at.	6	.015	5.6
X	Diundecylyl	0.9	Na	..	300	10	..	.10	22
XI	Dilauroyl	1.6	Na	..	300	2	0.5	.20	24

Reactions of Methyl-glyoxalidine.—To 5 g. of the base dissolved in chloroform was added a solution of bromine in the same solvent, with shaking and cooling, until the color remained. The heavy yellow precipitate was filtered off, washed with chloroform and dried in a vacuum desiccator. The yield was 11.9 g. or 82%. Analysis gave 65.23% of bromine; calculated for $C_4H_7N_2Br \cdot HBr$, 65.53. The product appears to be the hydrobromide of the brominated base.

Summary

The method of preparing methyl-glyoxalidine has been improved. Its homologs with normal alkyls have been made up to the undecyl. Their pharmacological properties have been determined.

BALTIMORE, MARYLAND RECEIVED SEPTEMBER 30, 1935

[CONTRIBUTION FROM THE HALL LABORATORY OF CHEMISTRY, WESLEYAN UNIVERSITY]

The Omega-Benzyl Derivatives of Acetophenone and their Reduction Products

BY G. ALBERT HILL AND A. J. COFRANCESCO

Although Haller and Bauer were not the first to prepare omega benzylated acetophenones, no earlier investigator produced these substances by the use of sodamide.[1,2] They did not, however, make tribenzylacetophenone. From our experience[3] with omega benzylated pinacolones, it was believed that tribenzylacetophenone could be synthesized by the sodamide method. As a consequence, it was decided that the preparation of the series of omega, mono-, di- and tri-benzyl acetophenones should be undertaken. Furthermore, it was decided to parallel our earlier investigation of the benzylpinacolone derivatives and to prepare, in addition to the ketones, their oximes, the corresponding carbinols and their phenylurethans, and also the hydrocarbons resulting from the replacement of each of the ketone oxygen atoms by two atoms of hydrogen.

Some trouble was experienced because the solvents employed in the ketone syntheses, ether, benzene, and toluene, seemed to form additive compounds with the first products of the reactions, the sodium derivatives of acetophenone, of monobenzylacetophenone, and of dibenzylacetophenone, respectively. This effect increased the viscosity of the systems to an extraordinary degree, making thorough mixing and temperature control difficult. These factors markedly affect the success of a given synthesis and may lead to the decomposition of the desired product when that has been formed.

Monobenzylacetophenone was prepared from sodamide, acetophenone, and benzyl chloride, in toluene, since the above-mentioned difficulties were minimized in this medium. Though odorless at first, the ketone developed fragrance on standing. This was probably caused by oxidation and splitting, an effect which is known to occur with dibenzyl ketone.[4] No attempt was made to isolate or to identify the odorous substances. With hydroxylamine, the ketone yielded a crystalline oxime.[5]

The secondary alcohol derived from monobenzylacetophenone had already been prepared

(1) Haller and Bauer, *Ann. chim.*, [8] **28**, 398 (1931).
(2) Haller and Bauer, *Bull. soc. chim.*, **31**, 1077 (1922).
(3) Hill and Bruce, THIS JOURNAL, **52**, 347 (1930).
(4) Fortey, *J. Chem. Soc.*, **75**, 871 (1899).
(5) Perkin and Stenhouse, *ibid.*, **59**, 1008 (1891).