NOTES

Reaction of Quinaldine with Aldehydes[1]

By Carl T. Bahner and Edwin S. Pace

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Continuing the search for additional compounds which are capable of damaging or inhibiting the growth of cancer cells *in vivo*[2] we have attempted to prepare substituted 2-(2-hydroxy-2-phenylethyl)-quinolines by condensation of quinaldine with substituted benzaldehydes[3,4] during long exposure to bright light[5] and also, in several cases, under similar conditions with light excluded. The absence of light did not seem to alter greatly the course of reaction. It was found that the rates of reaction to form the desired alcohols were in the order 2,4-dichlorobenzaldehyde > 3,4-dichlorobenzaldehyde > 2,6-dichlorobenzaldehyde > benzaldehyde, whereas 3,4-methylenedioxybenzaldehyde yielded the known 2-(3,4-methylenedioxystyryl)-quinoline[6] instead of the alcohol, and no crystalline alcohol was obtained from *p*-isopropylbenzaldehyde, anisaldehyde, 2,3-dimethoxybenzaldehyde, 2,3-diethoxybenzaldehyde, *p*-dimethylaminobenzaldehyde or 2-thiophenaldehyde. In the latter cases most of the starting material was recovered after several months by vacuum distillation, although there was in each case some dark, liquid residue in the distilling flask which may have contained some of the alcohol. In the case of 4-methoxybenzaldehyde a small amount of crystalline material melting at 127.5°, apparently 2-(4-methoxystyryl)-quinoline,[7] was isolated from the residue. These results tend to support the views of Phillips and Murphy[8] concerning the relation of structure of aromatic aldehydes to reactivity in such condensations.

Experimental

Equimolar quantities of the aldehydes and quinaldine were mixed with warming to obtain clear solutions, then allowed to stand at 40° in stoppered flasks, either exposed to ultraviolet light or protected from it.

2-[β-Hydroxy-β-(2,4-dichlorophenyl)-ethyl]-quinoline.—Crude yield 90%, m.p. 139–140° after recrystallization.

Anal.[9] Calcd. for $C_{17}H_{13}Cl_2NO$: C, 64.17; H, 4.12. Found: C, 64.10; H, 4.12.

2-[β-Hydroxy-β-(3,4-dichlorophenyl)-ethyl]-quinoline.—Yield purified crystals 22%, m.p. 154°.

Anal. Calcd. for $C_{17}H_{13}Cl_2NO$: C, 64.17; H, 4.12. Found: C, 64.45; H, 4.32.

2-[β-Hydroxy-β-(2,6-dichlorophenyl)-ethyl]-quinoline.—Yield purified crystals, 35%, m.p. 154°. *Anal.* Calcd. for $C_{17}H_{13}Cl_2NO$: C, 64.17; H, 4.12. Found: C, 64.05; H, 4.24.

Infrared absorption spectra for 50% Nujol mulls of these compounds and of 2-[β-hydroxy-β-phenylethyl]-quinoline were determined and are available on microfilm.[10] None of them were effective in inhibiting the growth of Sarcoma 180 in the Sloan–Kettering screening technique.

We wish to express our thanks to Samuel P. Sadtler and Son for determining the infrared absorption spectra, to the Sloan–Kettering Institute for Cancer Research for screening tests and to Miss Emma Brown and Mr. Charles L. Chumley, Jr., for assistance in carrying out some of the laboratory procedures.

(1) This research was supported in part by a grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

(2) C. T. Bahner, E. S. Pace and R. Prevost, This Journal, **73**, 3407 (1951).

(3) K. Loew, *Ber.*, **36**, 1666 (1903).

(4) H. Kaplan and H. G. Lindwall, This Journal, **65**, 927 (1943).

(5) A. Benrath, *J. prakt. Chem.*, [2] **73**, 386 (1906).

(6) M. Nencki, *Ber.*, **27**, 1977 (1894).

(7) O. Bialon, *ibid.*, **35**, 2786 (1902).

(8) A. P. Phillips and J. G. Murphy, *J. Org. Chem.*, **16**, 954 (1951).

(9) Analyses by Galbraith Laboratories, Knoxville, Tennessee.

(10) Order Document 3620 from American Documentation Institute, 1719 N Street, N.W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

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The Electrolytic Reduction of Homocystine at a Controlled Reference Potential

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The reduction of homocystine to homocysteine has previously been accomplished with tin and hydrochloric acid and by the action of sodium and liquid ammonia on the S-benzyl derivative.[2] As we are primarily interested in the application of electrolytic methods to the preparation of organic compounds, the preparation of homocysteine from homocystine by electrolytic reduction at a controlled reference potential was investigated. It was found that when the reduction was performed in a basic medium at a reference potential of −1.79 volts *vs.* a standard calomel electrode an almost quantitative yield of homocysteine, as determined titrimetrically, was obtained. However, because of the extreme ease with which homocysteine undergoes oxidation it was possible to isolate only 52.5% of the desired product.

Experimental

The electrolysis cell was a 1500-ml. beaker with a side arm extending to the base of the beaker through which was sealed a piece of platinum wire. This served as a contact for the mercury cathode which had an area of 95.03 sq. cm. In the beaker was placed a stirrer, thermometer, a standard calomel electrode which touched the mercury cathode surface, and an alundum membrane (fine porosity) 160 mm. high by 50 mm. diameter which served as an anode chamber. The anode consisted of a piece of platinum 10 cm. by 10 cm. Surrounding the cell was a cooling bath. The apparatus used for performing the reduction was the same as previously described.[3]

The catholyte was a solution of 94 g. of homocystine in 700 ml. of 1.25 *N* sodium hydroxide. The anolyte was a 1.25 *N* sodium hydroxide solution. At a reference potential *vs.* a standard calomel electrode of −1.79 volts the initial current density was 0.059 ampere per sq. cm. After four hours during which the temperature was maintained at 30–35° the current reached a plateau of 0.014 ampere per sq. cm. Iodimetric titration of the catholyte at this point indicated that there was a 100% reduction of the homocystine. The catholyte was cooled to 15°, rapidly adjusted

(1) Ciba Research Laboratories, Summit, New Jersey.

(2) B. Riegel and V. du Vigneaud, *J. Biol. Chem.*, **112**, 149 (1935).

(3) M. J. Allen, *Anal. Chem.*, **22**, 804 (1950); *Proc. Electrochem. Soc.*, Oct. (1951).

to *p*H 6.0 with concentrated hydriodic acid, filtered free of the homocystine which formed as a result of air oxidation, and then added to 3 liters of cold absolute ethanol. The precipitate was allowed to settle for several hours in a refrigerator, collected on a sintered glass filter and washed thoroughly with cold ethanol, yield 49 g. (52.5%). The product melted with decomposition at 234–235° (uncor.)[4] and was completely water soluble.

(4) V. Du Vigneaud, *ibid.*, **126**, 217 (1938).

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Formylation of Amines with Chloral and Reduction of the N-Formyl Derivatives with Lithium Aluminum Hydride

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A formylation procedure, which seems to be practically unknown, was discovered by Hofmann[2] in 1872. He found that ethylenediamine reacted energetically with chloral to produce chloroform and another liquid product which he assumed was N,N′-diformylethylenediamine since, by hydrolysis, it was converted into ethylenediamine and formic acid. He stated that treatment of ethylamine with chloral converted it into ethylformamide, and he also mentioned that formamide can be obtained by this process but that in this instance the process is not an advantageous one.

In a German patent,[3] issued in 1921, it was stated that when N-methyl-α-methylhomopiperonylamine[4] and chloral hydrate were mixed, a spontaneous reaction took place, and N-methyl-N-formylhomopiperonylamine[5] was obtained in almost quantitative yield. Piperidine and chloral hydrate reacted, at a temperature below 50°, to form the N-formyl derivative in 95% yield.

Since we have been unable to find any other instances in the literature in which N-formylation was achieved by the use of chloral, it seemed desirable to determine whether or not the method had a wide range of usefulness. It was found that formylation with the aid of chloral is an excellent general procedure for the acylation of a strong organic base. A rapid reaction takes place at a low temperature, chloroform is the only by-product and the formyl derivative usually is obtained in good yield. The 12 amines which were formylated in order to test the procedure are shown in Table I.

The reduction of two N-formyl derivatives, in excellent yields, to the N-methyl compounds, by the use of lithium aluminum hydride, has been reported.[6] The formyl derivatives, described in this paper, were reduced to the N-methyl derivatives in fair to good yields[7] with lithium aluminum hydride.

(1) American Foundation for Pharmaceutical Education Fellow.

(2) A. W. Hofmann, *Ber.*, **5**, 247 (1872).

(3) German Patent 334,555; *Frdl.*, **13**, 885.

(4) Homopiperonylamine is β-(3,4-methylenedioxyphenyl)-ethylamine.

(5) It is evident that an error was made either in the name of the initial product or in the name of the reaction product.

(6) J. Ehrlich, THIS JOURNAL, **70**, 2286 (1948); K. E. Hamlin and A. W. Weston, *ibid.*, **71**, 2210 (1949).

(7) We believe that in those instances in which the yields were below 80%, a further study, especially of the isolation procedures, would show that the yields could be increased.

TABLE I

N-FORMYL DERIVATIVES OF AMINES

	Derivative of	Yield, %	B.p., °C. Found	B.p., °C. Reported
1	Butylamine	83	122–123 (16 mm.)[a]	.....
2	Benzylamine	90	(M.p. 60–61°)[b]	(M.p. 49°)[c]
3	Cyclohexylamine	80	155–157 (22 mm.)	135–140 (10 mm.)[d]
4	β-Hydroxyethylamine	75	145–148 (0.5 mm.)	191–193 (10 mm.)[e]
5	β-Phenylethylamine	93	192–194 (20 mm.)	205 (15 mm.)[f]
6	Ethylenediamine[g]	95	(M.p. 110–111)	.....
7	Diethylamine	70	174–175 (745 mm.)	177–179 (atm.)[h]
8	N-Methyl-β-phenylethylamine	94	110–112 (1 mm.)[i]	.....
9	Pyrrolidine	65	87–89 (16 mm.)[j]	.....
10	3-Methylpyrrolidine	71	100–102 (16 mm.)[k]	.....
11	Piperidine	90	104–105 (16 mm.)	108 (14–15 mm.)[l]
12	Morpholine	95	229–232 (745 mm.)	234 (760 mm.)[m]

[a] *Anal.* Calcd. for $C_5H_{11}ON$: N, 13.84. Found: N, 13.65. [b] Recrystallized from petroleum ether (90–100°). [c] M. A. F. Holleman, *Rec. trav. chim.*, 13, 411 (1894). [d] German Patent 454,495 (1927); *Frdl.*, 16, 308. [e] H. Wenker, THIS JOURNAL, **57**, 1079 (1935). [f] A. Bischler and B. Napieralski, *Ber.*, 26, 1903 (1893). [g] N,N′-Diformyl. Recrystallized from ethyl acetate. *Anal.* Calcd. for $C_4H_8O_2N_2$: N, 24.10; Found: N, 24.02. In order to obtain ethylenediamine in anhydrous form, it was allowed to remain for some time over stick sodium hydroxide. It was then refluxed over sodium and distilled from the metal. [h] O. Wallach, *Ann.*, 214, 240 (1882). [i] *Anal.* Calcd. for $C_{10}H_{13}ON$: N, 8.58. Found: N, 8.43. [j] The hydrochloride was obtained by treatment of an ethereal solution of the formyl derivative with hydrogen chloride whereupon the salt precipitated; it is hygroscopic and decomposes in moist air; m.p. 92–94° after recrystallization from ethyl acetate. *Anal.* Calcd. for $C_5H_9ON\cdot HCl$: N, 10.33; Cl, 26.18. Found: N, 10.26; Cl, 26.02. [k] *Anal.* Calcd. for $C_6H_{11}ON$: N, 12.22. Found: N, 12.38. [l] O. Wallach and F. Lehmann, *Ann.*, **237**, 251 (1887). [m] Médard, *Bull. soc. chim.*, [5] 3, 1343 (1936).

The two-step methylation procedure which has been described should be useful for the methylation of acid- and/or heat-sensitive compounds, and in instances in which the ordinary methylation processes are unsatisfactory—for example, in the methylation of mezcaline.[8]

In order to obtain 3-methylpyrrolidine, itaconic acid was hydrogenated to methylsuccinic acid, the latter substance was converted into methylsuccinimide and the imide was reduced with lithium aluminum hydride to the pyrrolidine.

Experimental Part

Formylation.—The solid amine, dissolved or suspended in chloroform, or the liquid amine, was placed in a 3-necked flask fitted with a stirrer, dropping funnel and a condenser to which a calcium chloride tube was attached. The mixture was stirred, cooled in an ice-bath, and one molecular equivalent of chloral[9] was added, dropwise. The mixture was then stirred for several hours at room temperature, and finally heated for one-half hour on a steam-bath; the chloroform was then removed. Liquid products were purified by distillation, solid products by recrystallization.

Reduction of the Formyl Derivatives.—Lithium aluminum hydride (0.1 mole) and a suitable amount of absolute ether were placed in the apparatus described above. The flask was cooled in an ice-bath, the mixture was stirred and the formyl compound (0.1 mole), dissolved in ether, was added, dropwise. After the addition was completed, the mixture was stirred and refluxed for 6 hours. The flask was cooled in an ice-bath, the mixture was stirred rapidly and enough water was added, dropwise, to destroy the excess lithium aluminum hydride. After the material had

(8) L. Reti and J. A. Castrillon, THIS JOURNAL, **73**, 1767 (1951).

(9) Chloral was prepared by distillation from a mixture of equal weights of chloral hydrate and concentrated sulfuric acid.