dation; to convert pyruvic aldehyde to lactic acid; to increase the enolization of pyruvic acid; to increase the enolization of the acetol (Equations 6 and 7); and to lower the dissociation point of acetol (Equation 21).

5. The acetic acid yields reach a second maximum and the oxalic acid a second minimum in solutions with an initial concentration of potassium hydroxide approximating 0.5 *N*. These points are also a function of the temperature.

6. The effect of temperature on the yield of oxidation products varies in different regions of alkalinity.

7. The sources of oxalic and acetic acids have been shown.

In conclusion we wish to thank E. I. du Pont de Nemours and Company whose kindly interest and good will have made this work possible.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE EASTMAN KODAK COMPANY, No. 138]

THE 6-ALKYLOXYQUINALDINES

BY GURNEY O. GUTEKUNST AND H. LEB. GRAY

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The preparation of the 6-alkyloxyquinaldines involved the preparation of relatively large quantities of the various *p*-aminophenyl alkyl ethers. The problem can be attacked in two ways, namely, (1) the preparation of the *p*-nitrophenyl alkyl ethers and their subsequent reduction to the amino compounds, or (2) the preparation of the *p*-aceto-amino-phenyl alkyl ethers, and their hydrolysis by means of sulfuric acid.

We found that in some instances we obtained better yields by starting with the nitro compound, while in others it was advisable to proceed from the aceto-amino compound.

Several of the *p*-nitrophenyl alkyl ethers are described by Spiegel and Sabath[1] and Riess.[2] They were prepared by heating for 6 hours the potassium salt of *p*-nitrophenol in 16% alcoholic solution with the desired alkyl bromide or iodide in an autoclave at 170–180°.

We were able to prepare these ethers by boiling under a reflux condenser for 12 hours a solution of the potassium salt of *p*-nitrophenol in aqueous alcohol and the desired alkyl bromide or iodide. In a few cases the addition of the corresponding alcohol was necessary. The *p*-nitrophenyl butyl and *iso*-amyl and *p*-aminophenyl butyl and *iso*-amyl ethers have not been previously described.

Hinsberg[3] prepared *p*-aceto-aminophenyl-propyl ether and Jacobson[4]

[1] Spiegel and Sabath, *Ber.*, **34**, 1937 (1901).

[2] Riess, *ibid.*, **3**, 780 (1870).

[3] Hinsberg, *Ann.*, **305**, 283 (1899).

[4] Jacobson, *ibid.*, **287**, 182 (1895).

the *p*-aceto-aminophenyl benzyl ether. We were unable to find any reference to the other *p*-aceto-amino ethers in the literature.

The 6-methoxy and 6-ethoxyquinaldines have been mentioned several times in the literature,[5] but we were unable to find any reference to their method of preparation. We have confined this paper to a description of the higher homologs of the series. No mention is made in the literature of any of these higher 6-alkyloxyquinaldines. These quinaldines were all prepared according to the Doebner-Miller quinaldine synthesis. Several unsuccessful attempts were made to prepare the 6-benzyloxyquinaldine. In every method which we tried the benzyl group was hydrolyzed.

Experimental Part

A. Nitro- and Aminophenyl Ethers

***p*-Nitrophenyl Butyl Ether,** $p\text{-}NO_2C_6H_4OC_4H_9$.—One hundred and thirty g. of *p*-nitrophenol and 56 g. of potassium hydroxide were dissolved in 2 liters of 50% alcohol. Two liters of butyl alcohol and 184 g. of butyl iodide were added, and the mixture was boiled under a reflux condenser for 12 hours. The alcohol and water were evaporated on the water-bath, and the residue was extracted with ether. The ether solution was washed free from unchanged *p*-nitrophenol with dil. sodium hydroxide solution, and the ether solution dried over solid potassium hydroxide. The ether was distilled. A brown oil remained which solidified on cooling. This brown solid on recrystallizing from alcohol yielded fine white needles melting at 32°; yield, 108 g., or 55.38%.

Analysis. Calc. for $C_{10}H_{13}O_3N$: C, 61.5; H, 6.66; N, 7.21. Found: C, 61.2; H, 6.4; N, 7.16.

***p*-Aminophenyl Butyl Ether.**—Four hundred g. of stannous chloride was dissolved in 500 cc. of conc. hydrochloric acid, the solution heated to 85° and 100 g. of *p*-nitrophenyl butyl ether was added in small portions with constant stirring. The temperature of the mixture rose to 105°. After the addition of all the nitro ether, the reaction mixture was boiled for a short time and then allowed to cool. A solid white mass was obtained. This was made alkaline with sodium hydroxide and extracted with ether. The ether solution was dried over solid potassium hydroxide and the ether distilled. A brown oil remained, which was distilled under reduced pressure and gave a light-yellow oil boiling at 143–144° at 12 mm.; yield, 95.7%.

Analysis. Calc.: N, 8.48. Found: 8.30.

***p*-Nitrophenyl *Iso*-amyl Ether,** $p\text{-}NO_2C_6H_4OC_5H_{11}$.—One hundred and thirty nine g. of *p*-nitrophenol and 56 g. of potassium hydroxide were dissolved in 2 liters of 50% alcohol. Two liters of fusel oil and 155 g. of *iso*-amyl bromide were added, and the mixture was boiled under a reflux condenser for 12 hours. The *p*-nitrophenyl *iso*-amyl ether was purified in the same manner as was the previously described butyl ether. A brown oil remained on distilling the ether. After purification a pale-yellow oil was obtained boiling at 183° at 18 mm.; yield, 94.5 g., or 45.21%.

Analysis. Calc. for $C_{11}H_{15}O_3N$: C, 63.1; H, 7.1; N, 6.70. Found: C, 62.8; H, 7.08; N, 6.75.

The same method was successfully used for the preparation of *p*-nitrophenyl propyl, allyl, benzyl and *iso*butyl ethers.

***p*-Aminophenyl *Iso*-amyl Ether,** $p\text{-}NH_2C_6H_4OC_5H_{11}$.—This ether was obtained by the reduction of the nitro compound with stannous chloride and hydrochloric acid.

[5] Ger. pat., 167,770; *Phot. J.*, **60**, 183, 253 (1920).

It is a pale-yellow oil boiling at 149–150° at 15 mm. A yield of 94.52% was obtained.

Analysis. Calc. for $C_{11}H_{17}ON$: C, 73.7; H, 9.4; N, 7.82. Found: C, 73.5; H, 9.51; N, 7.74.

B. Aminophenyl Ethers

p-Aceto-aminophenyl Allyl Ether, p-$CH_3CONHC_6H_4OC_3H_5$.—One hundred and fifty-one g. of p-aceto-aminophenol and 56 g. of potassium hydroxide were dissolved in 2 liters of 75% alcohol, 121 g. of allyl bromide was added, and the mixture was boiled under a reflux condenser for 8 hours. The alcohol and water were evaporated on the water-bath, and the residue was extracted several times with ether. The ether solution was washed thrice with dil. sodium hydroxide solution to remove unacted upon p-aceto-aminophenol and the ether solution dried over solid potassium hydroxide. On distilling the ether a brown crystalline mass remained which was dissolved in the smallest possible amount of benzene, and petroleum ether added until no further crystals of the aceto-amino ether separated. The ether separated from benzene in minute crystals which melted at 88–89°; yield, 84 g., or 43.97%.

Analysis. Calc. for $C_{11}H_{13}O_2N$: C, 69.1; H, 6.8; N, 7.33. Found: C, 68.9; H, 6.7; N, 7.23.

p-Aminophenyl Allyl Ether, p-$NH_2C_6H_4OC_3H_5$.—The sulfate was prepared in a manner analogous to that described for the sulfate of the propyl ether. It crystallized in large white plates melting with decomposition at 244°. A yield of 92% was obtained.

One hundred and ninety-four g. of p-aminophenyl allyl ether sulfate suspended in 3 liters of hot water was made alkaline with sodium hydroxide. The free amine separated as a brown oil. The mixture was extracted with ether, and the ether solution dried over solid potassium hydroxide. The brown oil remaining, after evaporating the ether, was distilled under reduced pressure and yielded a light-yellow oil boiling at 143–144° at 13 mm.; yield, 90 g., or 61.69%.

p-Aceto-aminophenyl Butyl Ether, p-$CH_3COHNC_6H_4OC_4H_9$.—Two hundred g. of p-aceto-aminophenol and 72 g. of potassium hydroxide were dissolved in 2 liters of 50% alcohol, 2 liters of butyl alcohol and 260 g. of butyl iodide were added and the mixture was boiled under a reflux condenser for 6 hours. The purification of butyl ether was carried out in the manner described for the p-aceto-aminophenyl allyl ether. The butyl ether crystallized from benzol in the form of white needles melting at 112°; yield, 136 g., or 49.63%.

Analysis. Calc. for $C_{12}H_{17}O_2N$: N, 6.76. Found: 6.75.

p-Aminophenyl Butyl Ether, p-$NH_2C_6H_4OC_4H_9$.—The sulfate was prepared by hydrolyzing the aceto-amino ether with 20% sulfuric acid. It was obtained in the form of large white plates in 97.5% yield, and melted with decomposition at 270°.

The amino butyl ether was obtained from the sulfate, in a manner analogous to that for the amines previously described, as a light-yellow oil boiling at 143–144° at 12 mm.; yield, 81.03%.

Analysis. Calc. for $C_{10}H_{15}ON$: N, 8.48. Found: 8.30.

p-Aceto-aminophenyl Benzyl Ether, p-$CH_3COHNC_6H_4OCH_2C_6H_5$.—One hundred and fifty-one g. of p-aceto-aminophenol and 56 g. of potassium hydroxide were dissolved in two liters of 50% alcohol, 136 g. of benzyl chloride was added, and the mixture was boiled under a reflux condenser for 6 hours. The benzyl ether separated on cooling as white needles melting at 142°; yield, 115 g., or 47.71%.

p-Aceto-aminophenyl *Iso*-butyl Ether, p-$CH_3CONHC_6H_4OC_4H_9$.—p-Aceto-aminophenyl *iso*-butyl ether was prepared from alkaline aceto-aminophenol and *iso*-butyl iodide in a manner analogous to that used for the allyl ether. The *iso*-butyl ether crystallized in the form of white needles melting at 80–81°; yield, 33.8%.

Analysis. Calc. for $C_{12}H_{17}O_2N$: C, 69.5; H, 8.2; N, 8.48. Found: C, 69.5; H, 8.1; N, 8.21.

p-Aminophenyl *Iso*-butyl Ether,—The sulfate was prepared by boiling the aceto-amino ether with 20% sulfuric acid. It was obtained in 87% yield in the form of large white plates which decompose at 251–252°.

The free amine was obtained by suspending the sulfate in hot water and making strongly alkaline with sodium hydroxide. It is a colorless oil boiling at 145–146° at 10 mm.; yield, 82%.

p-Aceto-aminophenyl *Iso*-amyl Ether, p-$CH_3CONHC_6H_4OC_5H_{11}$.—The p-aceto-aminophenyl *iso*-amyl ether was prepared by boiling under a reflux condenser for 6 hours a solution of 151 g. of p-aceto-aminophenol and 56 g. of potassium hydroxide in 1 liter of water and 2 liters of alcohol with 165 g. of *iso*-amyl bromide. The purification was carried out in a manner similar to that used for the other aceto-amino ethers. The substance crystallized in white plates from benzol, melting at 103–103.5°; yield, 147 g., or 66.51%.

Analysis. Calc. for $C_{13}H_{19}O_2N$: N, 6.33. Found: 6.32.

p-Aminophenyl *Iso*-amyl Ether.—The sulfate was obtained as white plates, melting with decomposition at 253–254°; yield, 97%.

p-Aminophenyl *iso*-amyl ether is prepared from the sulfate in the same manner as were the previously described amines. It is a light-yellow oil boiling at 149–150°, at 15 mm.

C. Oxyquinaldine Derivatives

6-Propyloxyquinaldine, 6-$C_3H_7O.C_{10}H_8N$.—Two hundred g. of paraldehyde was slowly added to a well-stirred mixture of the hydrochloride of 100 g. of p-aminophenyl propyl ether and 300 g. of conc. hydrochloric acid. The mixture was heated on the water-bath for 6 hours and allowed to cool. It was then diluted to 3 liters with water and filtered from the tar which had formed. The filtrate was neutralized with sodium hydroxide solution, cooled and extracted with ether. The ether was evaporated from the ether extract and the residue heated on the water-bath with 5 g. of p-toluene-sulfochloride to remove primary and secondary amines. The resulting mixture was dissolved in 1:1 hydrochloric acid and filtered from the insoluble tar. The cold hydrochloric acid solution was then treated with a slight excess of sodium nitrite to remove the last traces of primary amines, heated on the water-bath and filtered. The filtrate was made alkaline with sodium hydroxide solution, extracted with ether and the ether solution dried over solid potassium hydroxide. A dark-brown oil remained on distilling the ether, which was distilled under reduced pressure and yielded the 6-propyloxyquinaldine as a light-yellow liquid boiling at 176–177°, at 16 mm.

Analysis. Calc. for $C_{13}H_{15}ON$: N, 6.96. Found: 6.82.

6-Propyloxyquinaldine Ethiodide, $C_3H_7OC_{10}H_6N(I)$ (C_2H_5).—A mixture of 6-propyloxyquinaldine and 10 g. of ethyl iodide was heated on the water-bath for 16 hours. The yellow crystalline mass which separated was dissolved in a small amount of alcohol and ether was added slowly until crystals began to form. The ethiodide crystallized from the ether-alcohol mixture in pale-yellow needles melting at 147.5°.

6-Allyloxyquinaldine, $C_3H_5OC_{10}H_8N$.—This quinaldine was prepared from p-aminophenyl allyl ether, paraldehyde and conc. hydrochloric acid exactly as described for the propyl oxyquinaldine. The method necessary for isolating the free base was decidedly different than for the propyl compound. The alkaline filtrate from the original reaction mixture yielded only a few drops of an oily substance. The original tar was then investigated. It was first covered with 1500 cc. of 30% sodium hydroxide solution and distilled with steam. A very few drops of oil distilled. The alkaline liquor

from the steam distillation was cooled, separated from the tar, and extracted with ether; 30 cc. of an oily liquid was obtained. This was purified with *p*-toluene sulfochloride, and finally with sodium nitrite as described for the propyl compound. A very small quantity of red, oily liquid was obtained on distilling the residue in a vacuum.

6-Allyloxyquinaldine Ethiodide, $C_3H_5OC_{10}H_5N(I)$ (C_2H_5).—The ethiodide of 6-allyloxyquinaldine was prepared analogously to the propyl compound. It separated from the ether-alcohol mixture in small yellow needles. These were contaminated with a small amount of a sticky material and all efforts at purification were unsuccessful.

6-Butyloxyquinaldine, $C_4H_9OC_{10}H_5N$.—The 6-butyloxyquinaldine was prepared in a manner analogous to that described for the preceding two oxyquinaldines. Its purification involved a somewhat different procedure from the others. No trace of the desired compound could be found in the filtrate from the original reaction mixture. A few drops of an oily liquid were obtained on distilling with steam the original tar in suspension in strong alkali, and on extracting the alkaline liquor thus obtained. The residual tar was finally subjected to distillation under reduced pressure, and yielded a considerable quantity of a black oil. An orange-colored oil was obtained from this on distillation in a vacuum, and was purified in the usual way by treating with toluene sulfochloride and with sodium nitrite. The 6-butyloxyquinaldine is an orange-colored crystalline solid boiling at 182–183°, at 13 mm. It is very soluble in all the ordinary organic solvents, and can be recrystallized from a small quantity of petroleum ether, from which it separates in little yellow nodules which soften at 48° and melt at 52°.

Analysis. Calc. for $C_{14}H_{17}ON$: N, 6.49. Found: 6.50.

6-Butyloxyquinaldine Ethiodide, $6\text{-}C_4H_9OC_{10}H_6N(I)$ (C_2H_5).—This ethiodide was prepared in the same way as were the previously described ethiodides. It crystallized from the ether-alcohol mixture in small yellow needles, melting at 186°.

6-*Iso*-butyloxyquinaldine, $6\text{-}C_4H_9OC_{10}H_5N$.—The 6-*iso*-butyl compound was prepared in a similar manner. The purification, however, was somewhat different. The alkaline filtrate from the original reaction mixture was extracted with ether and the ether extract saved. To the residual tar, 500 cc. of 40% sodium hydroxide solution and 2 liters of water were added, and the mixture was distilled with steam until no more oil came over. The distillate was then extracted with ether, the combined ether extracts were dried over solid potassium hydroxide and the ether was distilled. A thick black oil remained, which yielded a light-yellow oil on distilling under reduced pressure. The yellow oil was purified by treating with *p*-toluene sulfochloride and finally with sodium nitrite as previously described for the propyloxyquinaldine. The 6-*iso*-butyloxyquinaldine was obtained as a colorless, oily liquid boiling at 171–172°, at 12 mm.

6-*Iso*-butyloxyquinaldine Ethiodide, $C_4H_9OC_{10}H_5N(I)$ (C_2H_5).—Ten g. of 6-*iso*-butyloxyquinaldine and 10 g. of ethyl iodide were boiled under a reflux condenser for 12 hours, when a yellow crystalline solid separated. This was dissolved in alcohol and ether was added until crystals began to form. The ethiodide is obtained as little yellow needles melting at 142°.

6-*Iso*-amyloxyquinaldine, $C_5H_{11}OC_{10}H_5N$.—The 6-*iso*-amyloxyquinaldine was prepared in the same manner as was the propyl compound except that the paraldehyde was added slowly through the condenser to the hot mixture of the amine and hydrochloric acid. The base was retained in the residual tar, and was isolated as a black oil by distilling the tar under reduced pressure. This black oil, on being distilled in a vacuum, yielded a light yellow oil which was purified by treating with *p*-toluene sulfochloride and sodium nitrite as described for the propyl compound. The final product is obtained as a light yellow liquid boiling at 182–183° at 10 mm.

Analysis. Calc. for $C_{15}H_{19}ON$: N, 6.08. Found: 6.11.

6-*Iso*-amyloxyquinaldine Ethiodide, $C_5H_{10}C_{10}H_6N(I)$ (C_2H_5).—The ethiodide was

obtained analogously to the previously described ethiodides. It crystallizes from the ether-alcohol mixture in yellow needles melting at 201°.

Summary

1. A modified method is given for preparing the *p*-nitrophenyl alkyl ethers.

2. A method is described for preparing the *p*-aceto-aminophenyl alkyl ethers from *p*-aminophenol.

3. The following new compounds have been prepared: the *p*-nitrophenyl butyl-, and *p*-nitrophenyl *iso*-amyl ethers; the *p*-aceto-aminophenyl butyl-, *p*-aceto-aminophenyl allyl-, *p*-aceto-aminophenyl *iso*-butyl, *p*-aceto-aminophenyl *iso*-amyl ethers; the *p*-aminophenyl butyl- and *p*-aminophenyl *iso*-amyl ethers; and the sulfates of the *p*-aminophenyl alkyl ethers.

4. Several 6-alkyloxyquinaldines, and their ethiodides, have been prepared: 6-propyloxy-, 6-allyloxy-, 6-butyloxy-, 6-*iso*-butyloxy-, and 6-*iso*-amyloxyquinaldines.

We are indebted to Mr. B. V. Bush and Mr. P. A. Benedict for the analytical data given in this paper, and to Mr. S. Bissel for a part of the experimental work.

ROCHESTER, NEW YORK

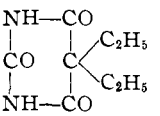
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

RESEARCHES ON HYDANTOINS. SYNTHESIS OF THE SOPORIFIC, 4,4-PHENYLETHYL-HYDANTOIN (NIRVANOL)

BY WILLIAM T. READ[1]

Received March 14, 1922

Pyrimidine derivatives have met with wide use as pharmaceuticals. The most important are the valuable soporifics, diethyl-barbituric acid (I) or Veronal, and phenylethyl-barbituric acid (II) or Luminal. As far as the writer is aware, the only hydantoin derivative of proved value as a soporific is 4,4-phenylethyl-hydantoin (III), now known by the trade name of Nirvanol.



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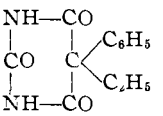

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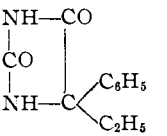

III

Since the grouping RR′—C—CO—NH—CO—NH— is common to the dialkyl pyrimidines of the barbituric acid series and the hydantoins sub-

[1] (This paper is constructed from a dissertation presented by William Thornton Read in June, 1921, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.—T. B. Johnson.)