sponding disulfides, sulfonic acids and related derivatives. The β-bromo-alkyl ethers may be used in the same way as ordinary alkyl halides in the malonic ester synthesis, Williamson's reaction and in the formation of ethoxy-alkylanilines.

β-Bromo-alkyl ethyl ethers react in ether solution with magnesium to form olefins. *Iso*heptene is prepared in this way.

COLUMBUS, OHIO

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[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY AT DUKE UNIVERSITY]

# PICTET AND GAMS' BERBERINE SYNTHESIS

BY JOHANNES S. BUCK AND ROSE M. DAVIS[1]

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The synthesis of the alkaloid berberine by Pictet and Gams[1a] has long been regarded as classic. Some doubt as to its accuracy has, however, recently arisen.

Buck and Perkin[2] in attempting to synthesize *epi*-berberine (2,3-dimethoxy-9,10-methylenedioxyprotoberberine)[3] by the method of Pictet and Gams[1] obtained only the isomeric pseudo-*epi*-berberine (2,3-dimethoxy-10,11-methylenedioxyprotoberberine). Haworth, Perkin and Rankin[4] in repeating Pictet and Gams' synthesis of berberine (2,3-methylenedioxy-9,10-dimethoxyprotoberberine) obtained exclusively the isomeric pseudoberberine (2,3-methylenedioxy-10,11-dimethoxyprotoberberine), the second ring closure taking place so as to give the 10,11- and not the 9,10-dimethoxy compound. A search of the literature showed that Pictet and Gams' alleged ring closure to give the 9,10 compound is unique, at least when the ring substituents are methoxyl or methylenedioxy groups. Pictet himself expresses astonishment that berberine and not the isomer should be formed. The only departure from the general rule is the formation of both tetrahydropalmatine and nor-coralydine from tetrahydropapaveroline, recorded by Späth and Kruta.[5] Here, however, hydroxyl, not alkoxyl, groups were the substituents.

It therefore appeared necessary to investigate the synthesis further, in order to detect any error, if such were present. The authors believe that they have definitely shown the synthesis to be erroneous.

Pictet and Gams[1] on heating homoveratroylhomopiperonylamine with

[1] The material presented in this paper is from a dissertation submitted by Rose M. Davis to the Graduate School of Arts and Sciences of Duke University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1929.

[1a] Pictet and Gams, *Ber.*, **44**, 2480 (1911).

[2] Buck and Perkin, *J. Chem. Soc.*, **125**, 1675 (1924).

[3] The nomenclature of Buck, Perkin and Stevens, *ibid.*, **127**, 1462 (1925), is used in the present paper.

[4] Haworth, Perkin and Rankin, *ibid.*, **125**, 1686 (1924).

[5] Späth and Kruta, *Monatsh.*, **50**, 341 (1928).

phosphorus pentoxide, obtained an amorphous glassy mass, melting at 68–70°, which they considered to be 6,7-methylenedioxy-3′,4′-dimethoxy-3,4-dihydroprotopapaverine. Haworth, Perkin and Rankin,[4] carrying out the same cyclization, obtained a white crystalline compound, melting at 88°, and this was shown[6] to be rapidly oxidized in air to give 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine. It may, therefore, be safely inferred that Pictet and Gams' product contained considerable amounts of this oxidized base, especially as it had been exposed in a desiccator. 6,7-Methylenedioxy-3′,4′-dimethoxy-3,4-dihydroprotopapaverine, as has clearly been shown by Haworth and co-workers,[4,6] gave only 6,7-methylenedioxy-3′,4′-dimethoxy-1,2,3,4-tetrahydroprotopapaverine on reduction, and this, on treatment with methylal or formaldehyde, results exclusively in 2,3-methylenedioxy-10,11-dimethoxytetrahydroprotoberberine (pseudoberberine). The obvious inference is that Pictet and Gams mistook tetrahydropseudoberberine for tetrahydroberberine. The authors constantly obtained tetrahydropseudoberberine on repeating Pictet and Gams' work. The other source of error is the presence of the oxidized cyclized material, which had been overlooked by Pictet and Gams. This has been shown by Buck and co-workers[6] (and carefully checked by the present authors) to give rise to 6,7-methylenedioxy-3′,4′-dimethoxy-9-ketoprotopapaverine under the action of alkalies, with surprising ease. As far as is possible to see from Pictet and Gams' meager account, this compound is identical with their "veratryl-nor-hydrohydrastinine," the supposed reduction product of 6,7-methylenedioxy-3′,4′-dimethoxy-3,4-dihydroprotopapaverine. The compound is incapable of reacting with methylal, the requisite imino group being absent. Pictet and Gams' analysis is correct for veratryl-nor-hydrohydrastinine.

It is true that Pictet and Gams reduced their crude cyclization product before treating it with alkali, but the authors have observed that 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine is not reduced under the conditions employed. It would seem highly probable, therefore, that Pictet and Gams obtained not veratryl-nor-hydrohydrastinine (6,7-methylenedioxy-3′,4′-dimethoxy-1,2,3,4-tetrahydroprotopapaverine) but 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine on cyclization, reduction and treatment with alkali. As before stated, this cannot react with methylal. It is concluded, therefore, that Pictet and Gams never isolated veratryl-nor-hydrohydrastinine, but obtained the oxidized side product, a compound closely related to xanthaline. Their tetrahydroberberine must, therefore, have been actually tetrahydropseudoberberine and have been obtained by operating with crude reaction mixtures.

[6] Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2176 (1924).

There remained one possibility, that Pictet and Gams had by chance obtained some unknown reduction product capable of giving tetrahydroberberine on treatment with methylal. The authors therefore carefully investigated the reduction products of 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine and of 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine. From the first, 6,7-methylenedioxy-3′,4′-dimethoxy-9-hydroxy-1,2,3,4-tetrahydroprotopapaverine was obtained and from the second, 6,7-methylenedioxy-3′,4′-dimethoxy-9-hydroxyprotopapaverine. This, analogous to the compound papaverinol described by Stuchlik,[7] cannot react with methylal. 6,7-Methylenedioxy-3′,4′-dimethoxy-9-hydroxy-1,2,3,4-tetrahydroprotopapaverine indeed reacts with methylal or formaldehyde, giving rise to an interesting compound described in the experimental part, but this compound is very different from the tetrahydroberberine.

## Experimental

Veratryl-nor-hydrohydrastinine (6,7-Methylenedioxy-3′,4′-dimethoxy-1,2,3,4-tetrahydroprotopapaverine).—The details given by Pictet and Gams regarding this compound are meager. A number of experiments, following as closely as possible the procedure given, were carried out with the uniform result that the material obtained on cyclizing homoveratroylhomopiperonylamine with phosphorus pentoxide and then reducing with tin and hydrochloric acid, detinning with hydrogen sulfide and liberating the bases by alkali, was found to be a mixture of 6,7-methylenedioxy-3′,4′-dimethoxy-1,2,3,4-tetrahydroprotopapaverine (melting at 84° and described by Haworth and co-workers[4,6]) and 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine, melting at 208°. The former has been dealt with in another place; the latter cannot react with methylal (this was checked experimentally).

Authentic 6,7-methylenedioxy-3′,4′-dimethoxy-3,4-dihydroprotopapaverine when reduced with tin and hydrochloric acid gave 6,7-methylenedioxy-3′,4′-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, melting at 84° (see above), together with varying amounts of 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine, melting at 151° and formed by air oxidation of unchanged material. If alkali had been used (sodium hydroxide) in liberating the base, then in place of the latter compound (and formed from it) 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine melting at 208° was found. Neither this nor the dihydro compound is capable of reacting with methylal.

Pictet and Gams' Preparation of Tetrahydroberberine.—The preparation of tetrahydroberberine described by Pictet and Gams was very carefully repeated a number of times, following the rather vague directions as closely as possible except that the reduction was carried out immediately on the cyclized product and no attempt was made to isolate the supposed veratryl-nor-hydrohydrastinine, m. p. 208° (see above). After cyclizing homoveratroylhomopiperonylamine, reducing, detinning and treatment of the base with methylal, the pseudotetrahydroberberine (2,3-methylenedioxy-10,11-dimethoxytetrahydroprotoberberine) of Haworth and co-workers, melting at 168°, was always obtained. Mixed with authentic tetrahydroberberine, m. p. 167°, the mixture showed a considerable depression (10°). If the original cyclization product had been kept in a desiccator, as described by Pictet and Gams, or any other oppor-

[7] Stuchlik, *Monatsh.*, 21, 814 (1900).

tunity for air oxidation given, then 6,7-methylenedioxy-3',4'-dimethoxy-9-keto-protopapaverine, m. p. 208°, was also found.

In connection with compounds of the foregoing types, the authors have frequently found that mixed melting point determinations of their salts, especially the picrates, are quite unreliable. This point seems to have escaped some workers.

**6,7 - Methylenedioxy - 3',4' - dimethoxy - 9 - hydroxy - 1,2,3,4 - tetrahydroprotopapaverine.**— 6,7 - Methylenedioxy - 3',4' - dimethoxy - 9 - keto - 3,4 - dihydroprotopapaverine was reduced in 10% sulfuric acid solution with powdered zinc, a little copper sulfate being added to the mixture. When the reaction slackened, the whole was heated on a water-bath for one hour. After cooling, the mixture was filtered and treated with sodium hydroxide solution to liberate the bases. A gummy crystalline mass separated and was carefully fractionated from alcohol. Three compounds were found: (1) unchanged material, (2) 6,7-methylenedioxy-3',4'-dimethoxy-9-keto-protopapaverine, melting at 208°, and formed from the unchanged material by the action of the alkali and (3) a base $C_{19}H_{21}O_5N$. The latter, 6,7-methylenedioxy-3',4'-dimethoxy-9-hydroxy-1,2,3,4-tetrahydroprotopapaverine forms white glittering broken prisms melting at 161–162° to a yellow liquid. It is moderately soluble in alcohol and benzene, readily soluble in chloroform and slightly soluble in ether. Acetic anhydride and hydrochloric acid give colorless solutions.

*Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.4; H, 6.1. Found: C, 66.3; H, 6.2.

It was not found possible to obtain the above compound by reduction with tin and hydrochloric acid, unchanged material being always recovered, although there was some destruction. The failure is doubtless due to the separation of the highly insoluble tin double salt.

The catalytic method of reduction of Adams and co-workers (hydrogen–platinum oxide) was found to give excellent results with acetic acid as solvent, four atoms of hydrogen being smoothly absorbed. No compound other than that described above was isolated.

**2,3 - Methylenedioxy - 10,11 - dimethoxy - 13 - hydroxytetrahydroprotoberberine.**— 6,7-Methylenedioxy-3',4'-dimethoxy-9-hydroxy-1,2,3,4-tetrahydroprotopapaverine, dissolved in methyl alcohol, was mixed with sodium bicarbonate and 40% formaldehyde solution gradually added. The mixture was heated on the water-bath and then precipitated with water and salt. The product was heated with concentrated hydrochloric acid for a few minutes. Upon cooling yellow crystals formed and these were recrystallized from hot dilute hydrochloric acid. These were decomposed with potassium carbonate solution and the product recrystallized from methyl alcohol. A mass of fine yellow needles separated, melting at 153°. When methylal was substituted for formaldehyde, the product was obtained with considerable difficulty and in very poor yield. It is readily soluble in chloroform, moderately soluble in alcohol and benzene and sparingly soluble in ether.

*Anal.* Calcd. for $C_{20}H_{21}O_5N$: C, 67.6; H, 5.9. Found: C, 67.5; H, 6.0.

The test suggested by Robinson[8] to distinguish between 1,2,3,4- and 1,2,4,5-ring closures was applied to the above compound and indicated it to be a 1,2,4,5-derivative.

**6,7 - Methylenedioxy - 3',4' - dimethoxy - 9 - hydroxyprotopapaverine.**—6,7-Methylenedioxy-3',4'-dimethoxy-9-keto-protopapaverine was reduced in hot acetic acid solution by the catalytic method of Adams. Two atoms of hydrogen (maximum) were absorbed. After diluting and filtering, excess of ammonia was added and the gummy product which separated was recrystallized several times from alcohol. The

[8] Haworth and Perkin, *J. Chem. Soc.*, **127**, 1448 (1925).

compound forms fine white needles from alcohol, melting at 161°. It is very soluble in chloroform, moderately soluble in benzene and fairly soluble in ether.

*Anal.* Calcd. for $C_{19}H_{17}O_6N$: C, 67.3; H, 5.0. Found: C, 67.3; H, 5.1.

## Summary

The synthesis of berberine described by Pictet and Gams is in all probability erroneous, the error arising from overlooking the 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine formed by air oxidation of their cyclized product. The "veratryl-nor-hydrohydrastinine" described by them is 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine, which cannot react with methylal. Any product which was obtained by the action of methylal must have been pseudoberberine and have been obtained by operating with crude reaction mixtures.

DURHAM, NORTH CAROLINA

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[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

# STUDIES IN THE DIPHENYL SERIES. SOME ARSENIC DERIVATIVES OF DIPHENYL

BY DAVID E. WORRALL

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Diphenyl, a substance now available in quantity at a low cost, is the starting point for the preparation of arsenic-containing compounds of possible therapeutic value. Yet despite the vast amount of attention received by arsenicals during the past two decades, apparently only one paper has appeared in the literature on diphenyl derivatives of arsenic. Adams and Bauer[1] developed a method of entering this series, using the method of Bart with benzidine. Consequently a study has been made of tri-biphenylarsine and related compounds.

The actual starting material used in this investigation was *p*-bromoaniline, which was converted into 4-bromodiphenyl through the diazo reaction.[2] A pure product was obtained, but the process is time consuming, especially if the bromo-aniline has to be prepared, and the final yield is not particularly inspiring. Since then 4-chlorodiphenyl has appeared in the market and at a price much lower than bromo-aniline. While only one experiment was conducted, chlorodiphenyl appeared to be just as effective as the bromo derivative for a synthetic reagent. Several general methods have long been known for the preparation of arylated arsenic from aryl halides. One of these was ruled out because of inability to obtain biphenylmercuric acetate, while poor results attended the use

[1] Adams and Bauer, THIS JOURNAL, **46**, 1925 (1924).

[2] Gomberg, "Organic Syntheses," John Wiley and Sons, Inc., New York, **1928**, Vol. VIII, p. **42**.