[CONTRIBUTION FROM THE CHEMICAL DEPARTMENT, UNIVERSITY OF BRISTOL]

A NEW METHYLATION PROCESS

BY M. NIERENSTEIN

RECEIVED JUNE 23, 1930 PUBLISHED OCTOBER 6, 1930

The catechins are remarkable for their well-crystallizing and sharp-melting penta-acetyl derivatives.[1] On the other hand, the corresponding methoxy derivatives, if prepared in the usual way by the action of dimethyl sulfate and alkali, either on the catechins themselves, or on the penta-acetyl derivatives, are contaminated with by-products, formed through fission of the chromane-ring.[2] It was therefore desirable to evolve a reliable method for the conversion of these well-defined penta-acetyl derivatives into the corresponding methoxy derivatives; such a method has now been elaborated. It consists in the interaction in the cold of diazomethane with these penta-acetyl derivatives in the presence of piperidine. The reaction proceeds smoothly and is easily controlled, each molecular proportion of piperidine removing one acetyl group, which is then replaced by the methyl group. The results obtained with the penta-acetyl catechins will be dealt with later on, a few representative cases being meanwhile described.

Experimental

The acetyl derivatives used in the following experiments were dissolved in alcohol and to this solution was added piperidine, also in alcoholic solution. Into this solution was then distilled an ethereal solution of diazomethane prepared from nitrosomethylurethan, the reaction being carried out in the apparatus previously described.[3] After standing for twenty-four hours the alcohol was removed, the solid dissolved in warm aqueous alkali and refluxed for thirty minutes on a water-bath. The methoxy derivatives were obtained by acidifying the cold solution, which had previously been freed from piperidine by exhaustive extraction with ether.

(1) **Veratric Acid.**—One gram of diacetyl-protocatechuic acid (m. p. 162°)[4] was reacted on with diazomethane from 5 cc. of nitrosomethylurethan in the presence of 1 g. of piperidine (excess); yield, 0.6 g.; m. p. and mixed m. p., 180°.

Anal. Subs., 2.107, 6.302 mg.: AgI, 5.365, 16.267 mg. Calcd. for $C_9H_{10}O_4$: OCH_3, 34.07. Found: OCH_3, 33.61, 34.06.

(2) **Isovanillic Acid.**—The same proportions as given above were used, with the exception of piperidine, when 0.4 g. (1 mol) was added; yield, 0.7 g.; m. p. 249°.

Anal. Subs. 4.085 mg.: AgI, 5.667 mg. Calcd. for $C_8H_8O_4$: OCH_3, 18.45. Found: OCH_3, 18.32.

(3) **Dimethyl-β-resorcylic Acid.**—One gram of diacetyl-β-resorcylic acid (m. p.

---

[1] Nierenstein, *J. Indian Chem. Soc.*, 7, 279 (1930).

[2] Nierenstein, THIS JOURNAL, 48, 1964 (1926).

[3] Malkin and Nierenstein, *ibid.*, 52, 1508 (1930).

[4] Malkin and Nierenstein, *Ber.*, 61, 797 (1928).

137°)[5] was reacted on with diazomethane in the presence of 0.8 g. (2 mols) of piperidine; yield, 0.5 g.; m. p. 109°, which is in agreement with the melting point given by Liebermann and Lindenbaum.[6]

Anal. Subs., 3.314 mg.: AgI, 8.533 mg. Calcd. for $C_9H_{10}O_4$: OCH_3, 34.07. Found: OCH_3, 33.99.

(4) **Monomethyl-β-resorcylic Acid.**—When using one molecule of piperidine a mixture of the two monomethyl-β-resorcylic acids was obtained. This mixture melted gradually between 169 and 174°, and gave with ferric chloride a violet coloration which had a distinctly greenish tint. The two isomers in question show the following properties: 2-hydroxy-4-methoxybenzoic acid melts at 160–161°, and gives a violet coloration with ferric chloride, whereas 2-methoxy-4-hydroxybenzoic acid melts at 187–189°, and gives a red-brown coloration with ferric chloride. The former substance therefore predominated in the mixture.

Anal. Subs., 7.310 mg.: AgI, 10.571 mg. Calcd. for $C_8H_8O_4$: OCH_3, 18.45. Found: OCH_3, 19.08.

(5) **Trimethylgallic Acid.**—One gram of triacetylgallic acid (m. p. 175°)[7] was methylated in the presence of an excess of piperidine; yield, 0.8 g.; m. p. 169°, with slight evolution of carbon dioxide.

Anal. Subs., 4.017 mg.: AgI, 13.303 mg. Calcd. for $C_{10}H_{12}O_5$: OCH_3, 43.86. Found: OCH_3, 43.72.

Summary

A method is described for the replacement of acetyl groups by methyl groups, using diazomethane and piperidine.

Bristol, England

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

LOCAL ANESTHETICS DERIVED FROM QUINOLINE AND ISOQUINOLINE

By C. F. Bailey and S. M. McElvain

Received June 23, 1930 Published October 6, 1930

Several previous communications[1] from this Laboratory have described the preparation of substituted piperidino-alkyl benzoates and substituted piperidino-alkyl cinnamates. Since these compounds possessed local anesthetic action, some of them to a marked degree, it seemed desirable to prepare for pharmacological study a series of hydroquinolino-alkyl benzoates in which the nitrogen, instead of being a member of a piperidine ring, is incorporated in a bicyclic structure such as that present in certain of the reduced forms of quinoline and isoquinoline. It seemed of par-

[5] Bergmann and Dongschat, *Ber.*, 52, 179 (1919).

[6] Liebermann and Lindenbaum, *ibid.*, 41, 1613 (1908).

[7] Fischer, Bergmann and Lipschitz, *ibid.*, 51, 53 (1918), give m. p. 171–172° (corr.) for triacetylgallic acid.

[1] McElvain, This Journal, 49, 2835 (1927); Thayer and McElvain, *ibid.*, 50, 3348 (1928); Bailey and McElvain, *ibid.*, 52, 1633 (1930); Bailey and McElvain, *ibid.*, 52, 2007 (1930).