acetic acid solution; and H, replacement of an amino group by halogen through the Sandmeyer reaction. Other explanatory comments are given in the footnotes.

Summary

The study of the orienting effect of the methoxy group in phenyl ether derivatives has been extended. In determining this orientation a group of new compounds has been prepared and the structure of each proved.

LAWRENCE, KANSAS RECEIVED AUGUST 4, 1939

[CONTRIBUTION FROM THE ORGANIC LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XVIII. Synthesis of Substituted Piperazines and the Hydrolysis of Amines

BY J. P. BAIN[1] AND C. B. POLLARD

It has been shown that N-phenylpiperazine[2] may be prepared readily by heating a mixture of aniline and diethanolamine hydrochlorides. We have found that this method cannot be extended conveniently to the preparation of C-substituted piperazines from arylamines and diisopropanolamine. We have shown that piperazines may be prepared from amino alcohols[3] using the catalytic alkylation methods of Paden and Adkins[4] and Hill and Adkins.[5] This paper reports an extension of the synthesis of piperazines by this method and the formation of alcohols by hydrolysis of amines under catalytic alkylation conditions. This interesting side reaction does not appear to have been reported by other investigators.

Experimental

N-Cyclohexylamines were prepared by passing ethylene oxide into a methanol solution of cyclohexylamine. After removal of the solvent at atmospheric pressure the amino alcohols were distilled at 10 mm. pressure. N-Cyclohexylethanolamine distilled at 118° and N-cyclohexyldiethanolamine at 175°. The neutral equivalents of these compounds were determined using methyl red as the indicator: N-cyclohexylethanolamine, neut. equiv. calcd. 143.2, found 143.0; $n^{25}D$ 1.4842; N-cyclohexyldiethanolamine, neut. equiv. calcd. 187.3, found 187.2; $n^{25}D$ 1.4927.

N-Phenyldiisopropanolamine was prepared by heating one mole of aniline with two moles of propylene oxide in 300 cc. of dioxane to 170° in a bomb for several hours. The product was a viscous straw-colored liquid boiling at 184–185° at 10 mm.; N calcd. 6.69, found 6.60.

N-*p*-Tolyldiisopropanolamine was prepared similarly. After removal of solvent the product solidified and was recrystallized several times from hexane and from diisopropyl ether as slightly pink needles, m. p. 112°; N calcd. 6.27, found 6.20.

1,4-Dicyclohexylpiperazine was prepared by two methods. (a) Six hundred ml. of dioxane containing 1 mole each of cyclohexylamine and N-cyclohexyldiethanolamine was heated to 250–270° and shaken for three to four hours in hydrogen at a pressure of 34 atmospheres with 25 g. of copper–chromium oxide catalyst. After filtration from the catalyst and removal of the dioxane, the reaction mixture was distilled at 10 mm. pressure. The first fraction of 20 g., boiling at 60–61°, was identified as cyclohexanol by conversion to the phenylurethan, m. p. 82.5°. The second fraction, 19 g., boiling at 109–110°, was not identified. The third fraction, distilling between 170° at 10 mm. and 200° at 5 mm. partly solidified on cooling. Recrystallized first from pentane and then from aqueous methanol it yielded the piperazine in 20% yield, m. p. 118°. For analysis it was converted to the sparingly soluble dihydrobromide: Br calcd. 38.77, found (gravimetric) 38.76, neut. equiv. calcd. 206, found (by titration with phenolphthalein in the presence of benzene to remove the free amine as formed). (b) Cyclohexylethanolamine treated under the same conditions gave the piperazine in the same yield as well as the two low boiling fractions.

1-Cyclohexyl-2,6-dimethyl-4-phenylpiperazine, b. p. 205–210° at 2 mm., was prepared in 20% yield from cyclohexylamine and N-phenyldiisopropanolamine. The dihydrobromide was used for analysis: N calcd. 6.45, found 6.41; Br calcd. 36.81, found 36.83.

1-Cyclohexyl-2,6-dimethyl-4-*p*-tolylpiperazine, prepared from cyclohexylamine and N-*p*-tolyldiisopropanolamine, boiling at 175–230° at 5 mm., 15% yield, was converted to the hydrobromide and recrystallized from water; for the monohydrobromide, Br calcd. 21.72, found 21.67.

Cyclohexanol from Cyclohexylamine.—Sixty grams of cyclohexylamine, 300 ml. of dioxane, 20 ml. of water and 20 g. of copper–chromium oxide catalyst were placed in a bomb under 500 lb./sq. in. (34 atm.) hydrogen pressure and heated at 260–270° for four hours with shaking. After removal of low boiling material the product was fractionated at 10 mm. The fraction boiling at 55–65° was acidified and the neutral material extracted with ether. The neutral material distilled at 60–61° at 10 mm. and was identified as cyclohexanol by conversion to the phenylurethan, m. p. 82.5°. The yield of the pure alcohol was 20%.

(1) This paper is abstracted from a portion of a dissertation submitted by J. P. Bain to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy, May, 1939.

(2) Pollard and MacDowell, THIS JOURNAL, **56**, 2199 (1934).

(3) Bain and Pollard, *ibid.*, **61**, 532 (1939).

(4) Paden and Adkins, *ibid.*, **58**, 2487 (1936).

(5) Hill and Adkins, *ibid.*, **60**, 1033 (1938).

Diethylcyclohexylamine was prepared from cyclohexylamine and diethyl sulfate. Primary and secondary amines were removed with benzenesulfonyl chloride. The product boiled at 68.5–69 at 10 mm.; neut. equiv. calcd. 155.3, found 156.1.

Cyclohexanol was prepared from diethylcyclohexylamine in 33% yield under the conditions used for the hydrolysis of cyclohexylamine. Seventy-eight grams of diethylcyclohexylamine was treated with 300 ml. of 50% aqueous dioxane and 23 g. of copper–chromium oxide catalyst at 270–280° without hydrogen pressure. The product boiling at 50–68° at 10 mm. was acidified and extracted with ether. Only about 1 g. of neutral material was obtained. The amine hydrochlorides were treated with alkali and the free amines fractionated at 10 mm. The fraction boiling at 53.5–56° weighed 12 g. and gave a neutral equivalent of 133.0 (calculated for mono- and diethylcyclohexylamines, 127.2 and 155.3, respectively). This product on treatment with sodium nitrite and hydrochloric acid yielded 5 g. of a pale yellow oil, b. p. 127–128° at 12.5 mm. The literature[6] gives 130° at 12 mm. as the boiling point of N-nitrosoethylcyclohexylamine.

Summary

1. A number of new piperazine derivatives have been prepared from amino alcohols by catalytic alkylation.

2. The formation of alcohols from amines under catalytic alkylation conditions has been reported. This side reaction may account in part for the poor yields obtained in certain alkylations.

3. The generality and applicability of this reaction is being studied.

(6) Heilbron, "Dictionary of Organic Compounds," Vol. II, 1936, p. 27.

GAINESVILLE, FLORIDA RECEIVED JULY 13, 1939

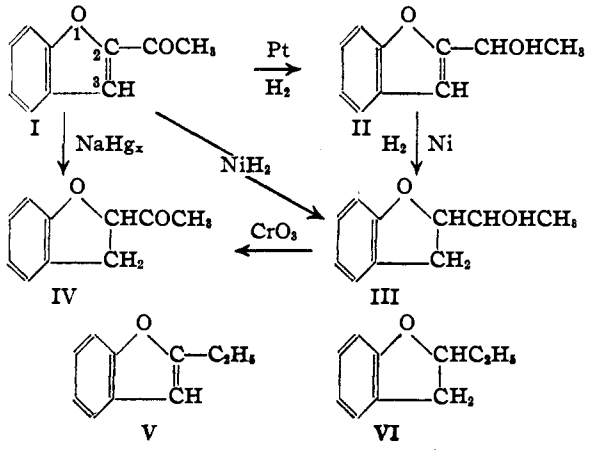
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Derivatives of Coumaran. VI. Reduction of 2-Acetobenzofuran and its Derivatives

BY R. L. SHRINER AND JOHN ANDERSON

In an investigation concerned with the preparation of 2-substituted coumarans, the catalytic hydrogenation of 2-acetobenzofuran and some of its derivatives was studied.

It has been found possible to obtain the two alcohol reduction products of 2-acetobenzofuran (I) by catalytic hydrogenation provided the appropriate catalyst is employed. Hydrogenation with a platinum catalyst results in the formation of 2-(1-hydroxyethyl)-benzofuran (II) while a Raney nickel catalyst leads to the formation of 2-(1-hydroxyethyl)-coumaran (III). The coumaran (III) also can be obtained from the benzofuran (II) by hydrogenation in the presence of Raney nickel.



Hydrogenation in the presence of colloidal platinum resulted in a mixture of II, III, 2-ethylbenzofuran (V) and 2-ethylcoumaran (VI). No 2-acetocoumaran (IV) was found among the products of catalytic reduction. A sample of this ketone was made by oxidation of the alcohol (III) and by a sodium amalgam reduction of 2-acetobenzofuran. It was characterized by its semicarbazone.

The catalytic reduction of 2-acetobenzofuran thus follows a course different from that of the closely related benzalacetone, which is smoothly reduced to benzylacetone[1] first and then undergoes further reduction to 4-phenyl-2-butanol. The results constitute further evidence that catalytic hydrogenation of α,β-unsaturated ketones occurs by 1,2-addition[1] and not by 1,4-addition[2] as is the case in reduction by chemical means.[3] In this particular case the double bond in the 2,3-position probably is stabilized to some extent by resonance in the benzofuran nucleus.

ω-Acetoxy-2-acetobenzofuran (VIII) was prepared by bromination of 2-acetobenzofuran, followed by treatment of the resulting ω-bromo-2-acetobenzofuran (VII) with sodium acetate.

An unusual reaction took place when ω-acetoxy-2-acetobenzofuran (VIII) was subjected to

(1) Kern, Shriner and Adams, THIS JOURNAL, 47, 1147 (1925).
(2) Straus and Grindel, *Ann.*, 439, 276 (1924).
(3) Conant and Cutter, *J. Phys. Chem.*, 28, 1105 (1924).