2.5 g. of 2,5-dimethyl-3-aminofuran was diazotized in 50 cc. of alcohol containing 7 cc. of sulfuric acid and 10 cc. of water. Addition of copper powder caused vigorous evolution of a gas, which must have contained some nitric oxide since it turned brown on contact with air. After fifteen minutes in the ice-bath, the mixture was warmed cautiously on a steam-bath. Neither 2,5-dimethylfuran nor the product of ring opening, acetonylacetone, could be detected in the reaction mixture. Control experiments indicated that a quantity of dimethylfuran corresponding to a 5% yield in the replacement reaction could have been detected.

Summary

Methods have been developed for the synthesis of aminofurans. Two simple β-aminofurans, 2-methyl-3-aminofuran and 2,5-dimethyl-3-aminofuran, have been prepared in a pure state and their chemical behavior has been investigated.

The amines were found to resinify upon exposure to air, and to undergo hydrolytic cleavage on warming with aqueous acids or alkalies. The amines have been diazotized and coupled with β-naphthol, but other reactions of the diazotized amines appear to be abnormal.

The behavior of the 3-aminofurans indicates that they possess only to a limited extent the properties that are most typical of aromatic amines. The furan nucleus appears to have weakly aromatic properties rather than superaromaticity.

ITHACA, NEW YORK RECEIVED AUGUST 4, 1937

[CONTRIBUTION FROM THE PRESBYTERIAN HOSPITAL, COLUMBIA PRESBYTERIAN MEDICAL CENTER]

The Synthesis of Conjugated Bile Acids. IV. The Bondi and Mueller Procedure

BY FRANK CORTESE

We are now able to furnish practical details for a successful accomplishment of the old Bondi and Mueller[1] procedure in the synthesis of conjugated bile acids. The present revised methods offered are more convenient to carry out than the synthesis we have already published.[2]

Experimental Part

Ethyl Cholate.—Ten cc. of colorless C. P. fuming sulfuric acid (20–30% SO_3) is added to 250 cc. of commercial absolute alcohol previously cooled to 0°. The mixture is shaken with 25 g. of C. P. cholic acid for two hours or until solution occurs. After standing for twenty-four hours at room temperature, or in the ice-box on very warm days, the mixture is cooled to 0° and poured slowly, in portions and with stirring, into an ice-cold solution of 20 g. of sodium hydroxide in 2000 cc. of water, previously sprinkled with ethyl cholate. It is well to wait a few minutes until each added portion crystallizes in order to avoid large lumps. Fifty cc. of ethyl acetate is now stirred in well to neutralize the excess alkali. After standing in the refrigerator for ten or more hours, the product is filtered by *gentle* suction, washed well with water, thoroughly dried over calcium chloride in a vacuum desiccator, and dissolved in 200 cc. of boiling ethyl acetate. Enough petroleum ether (30–60°) is added to the hot solution to make a final volume of one liter. After twenty-four to forty-eight hours, but not longer, at room temperature, the product is washed on the filter with the same solvent mixture and air dried; yield, 22–24 g. (82–90%); m. p. 162–163°.[3]

Methyl Cholate.—The preparation is the same as the preceding except for the substitution of methyl alcohol as the solvent. The crude product, 25.8 g., is dissolved in 150 cc. of hot 95% alcohol. After cooling, 225 cc. of water is added. When crystals appear, the mixture is stored at 0° for twenty-four hours; yield 25 g.; m. p. 155–156°. (It is heated slowly between 90–105°.)

Ethyl Deoxycholate.—To a filtered solution of the crude product, prepared in the same way as ethyl cholate, in 85 cc. of ether (a cover glass is put on the gravity filter to prevent clogging) is added 265 cc. of light petroleum ether or enough to cause incipient cloudiness. The crystals are filtered, after forty-eight hours at room temperature, washed with a mixture of petroleum ether and ether (10:1) and air dried. The filtrate is spontaneously evaporated and only the dry material under the ring of gum is recrystallized. The total product is crystallized once more; yield, 23–25 g. (90%); m. p. 98–99°.

Cholyl Hydrazide.—Ten grams of pure ethyl cholate is refluxed for twenty-four hours with 8 cc. of commercial absolute alcohol and 4 cc. of hydrazine hydrate, excluding moisture with a calcium chloride tube. After diluting with 100 cc. of hot 95% alcohol, enough boiling water is added to make a total volume of 750 cc. The mixture is seeded, stirred well and stored at 0° for twenty-four hours. The product, filtered by gentle suction, washed with water and air dried for two days, should be completely soluble in very dilute hydrochloric acid: yield, 8.5 g. (88%); m. p. 188–189°.

Increasing the amount of hydrazine or the time of refluxing or the temperature results in the formation of a by-product insoluble in acid, presumably the symmetrically disubstituted hydrazide. Reducing the amount of hydrazine produces a lower yield and may give an inferior product.

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(1) Bondi and Mueller, *Z. physiol. Chem.*, **47**, 499 (1906).

(2) Cortese and Bashour, *J. Biol. Chem.*, **119**, 177 (1937).

(3) All melting points given in this article are corrected.

Deoxycholyl Hydrazide.—The refluxing period is six hours. If crystallization should occur before that time, more alcohol is used, but the addition is made sparingly to avoid a low yield. The reaction mixture is spontaneously evaporated, the residue thoroughly dried in a vacuum desiccator and refluxed with 50 cc. of ethyl acetate for thirty minutes in a flat-bottomed flask placed in a water-bath. After thoroughly crushing the material, refluxing is continued for one hour. The product, stored at 0° for twenty-four hours, washed with ethyl acetate and air dried, also should be completely soluble in acidulated water; yield, 8.9 g. (92%); sinters 202°, m. p. 210°.

Cholyl and Deoxycholyl Azides.—To a *complete* solution of 5 g. of hydrazide in 150 cc. of water and 1.5 cc. of concentrated hydrochloric acid, cooled to 0–2°, is added, slowly and with good stirring, an ice-cold solution of 1 g. of sodium nitrite in 10 cc. of water. Excess nitrous acid is confirmed with starch–iodide paper. Filtering on a large funnel with *gentle* suction is commenced after a total elapsed time of fifteen minutes. Large pieces of ice are kept in the filter, and the product is washed free from acid with ice water. The ice pieces are to be removed afterward to avoid undue dilution of the coupling mixture.

Sodium Taurocholate.—The fresh moist azide, described above, is suspended in an ice-cold mixture of 125 cc. of water and 17.5 g. of taurine. With gentle mechanical stirring, 30 cc. of ice-cold normal sodium hydroxide is added at 8–14° at the rate of 1.25 cc. every minute. (The addition is made all at once and is proportionately smaller for smaller runs.) Stirring is continued for forty-five minutes longer at the same temperature. After filtering, cooling to 0°, neutralizing to litmus with concentrated hydrochloric acid (15 drops), the solution is saturated with sodium chloride and ether, seeded, stored at 0° for twenty-four hours, shaken well, and kept cold for another day. The crystals are filtered by gentle suction, washed with ice-cold saturated salt solution saturated with ether, dried over calcium chloride and extracted with 75 cc. of commercial absolute alcohol. After adding 10 cc. of water, enough ether to cause incipient cloudiness, and a few crystals of product, the mixture is stored overnight at 0°. Enough ice-cold ether is added now to make 250 cc. The crystals are washed with ether followed by petroleum ether and air dried; yield, 4.5–4.8 g. (70%). It may be purified by reprecipitation with sodium chloride and ether, etc., with a recovery of 85%. We again emphasize that crystallization will not occur unless enough water is present,[2] $[\alpha]^{23}_{\mathrm{D}}$ +23.6° (*c*, 2.5, water) (Tanaka,[4] $[\alpha]^{20}_{\mathrm{D}}$ +23.9°). The sample was allowed to come to equilibrium with the prevailing atmospheric humidity and a separate moisture determination was made at the time of weighing.[2]

Sodium Taurodeoxycholate.—After the addition of the alkali, stirring is continued for twenty-five minutes at 8–14°. The reaction mixture is then allowed to rise to room temperature while stirring for an additional hour, filtered, cooled to 0°, neutralized and evaporated in a thin layer over calcium chloride in a vacuum desiccator. The pulverized residue is extracted with 75 cc. of 95% alcohol. After adding enough ether to incipient cloudiness and seeding, the solution is kept at room temperature for twenty-four hours. More ether is added similarly until a total volume of 250 cc. is attained. The product is washed with ether, followed by petroleum ether and then dried in a desiccator; yield, 6 g. (88%). It is purified by dissolving in sixteen times its weight of water, heating to 95° and stirring in 2 g. of sodium chloride for every gram of product. The slightly turbid solution is allowed to cool slowly. After two hours it is put in the refrigerator for one hour. The clear liquid is poured out, the hard gum dried over calcium chloride, extracted with alcohol, etc. The recovery is excellent. Salting out with sodium hydroxide at 60° is valuable for material that is slightly colored or refuses to crystallize,[2] $[\alpha]^{21}_{\mathrm{D}}$ +33.8° (*c*, 2.4, water)[5] (Wieland,[6] $[\alpha]^{15}_{\mathrm{D}}$ +33°). Larger runs may be worked up by employing acetone and concentrating under reduced pressure as outlined before.[2]

Glycocholic Acid.—The fresh cold moist azide is suspended in an ice-cold mixture of 25 g. of glycine and 100 cc. of water. The reaction is carried out as described under sodium taurocholate. After filtration, the product is precipitated ice cold with concentrated hydrochloric acid to a faint congo reaction. After keeping cold overnight, the product is washed well with water, dissolved in 25 cc. of hot 95% alcohol, and the solution is diluted with 225 cc. of water, stirred well and stored at 0° for twenty-four hours; yield, 4.8 g. (82%).

Sodium Glycocholate.—The free acid is dissolved in the calculated amount of normal sodium hydroxide, adjusting the *p*H to 8.3 by using a spot plate and a mixed indicator or phenolphthalein solution. The solution can absorb considerable quantities of the free acid. The residue obtained by evaporation over calcium chloride in a vacuum desiccator is dissolved in hot 95% alcohol, 25 cc. per gram. After adding one and one-half volumes of ether to the hot solution, it is stored in the ice box. The yield, washed with ether and air dried, is excellent $[\alpha]^{24}_{\mathrm{D}}$ +32.0°, 27.6° (*c*, 1.0, 2.5, water) (Josephson,[7] +32.00°, 27.80°).

Glycodeoxycholic Acid.—The reaction mixture is similar to the one used for glycocholic acid but the reaction is carried out as described under sodium taurodeoxycholate. The crude moist product, isolated as described under glycocholic acid, is dissolved in 35 cc. of hot 95% alcohol; the solution is diluted with 140 cc. of water previously saturated with 10 cc. of ether, and stored at 0°. It should now be filtered by gravity; yield, 4.8 g. (83%). It may be purified through the sodium salt.

Sodium Glycodeoxycholate.—The salt is made as described under sodium glycocholate, except that the solution shows very little tendency to dissolve excess free acid and therefore must be filtered from the suspension. For every gram of dried residue are used 15 cc. of boiling 95% alcohol and 20 cc. of ether: $[\alpha]^{21}_{\mathrm{D}}$ +44.9°, 39.6° (*c*, 1.03, 2.53, water).

Taurine and glycine may be recovered from residues according to suggestions outlined in previous papers in this series.

Summary

Practical procedures are detailed for the preparation of ethyl cholate, methyl cholate, ethyl

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[4] Tanaka, *Z. physiol. Chem.*, **220**, 39 (1933).

[5] We favor the present value rather than the one previously published.

[6] Wieland, *Z. physiol. Chem.*, **106**, 181 (1919).

[7] Josephson, *Biochem. J.*, **29**, 1484 (1935).

deoxycholate, cholyl hydrazide, deoxycholyl hydrazide, cholyl azide, deoxycholyl azide, sodium taurocholate, sodium taurodeoxycholate, glycocholic acid, sodium glycocholate, glycodeoxycholic acid, and sodium glycodeoxycholate.

NEW YORK, N. Y. RECEIVED OCTOBER 8, 1937

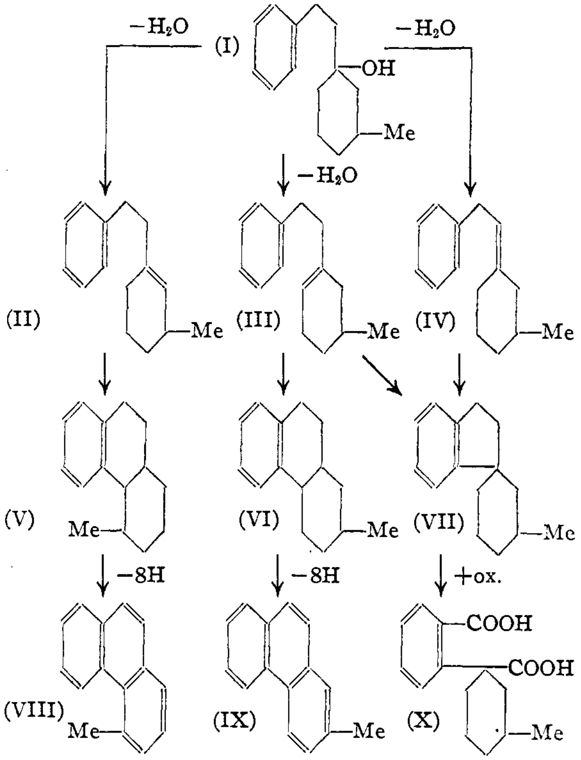
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY AND THE COLLEGE OF THE CITY OF NEW YORK]

The Dehydration of Beta-Phenylethyl-3-methylcyclohexanol-1

BY DAVID PERLMAN AND MARSTON TAYLOR BOGERT

β-Phenylethyl-3-methylcyclohexanol-1 (I) lends itself to an interesting study in cyclodehydration, with results which support Wallach's findings[1] that 1,3-dimethylcyclohexanol-3, when dehydrated by dilute sulfuric acid, yielded 1,3-dimethylcyclohexene-3, except that, under the conditions of our experiments, the olefin formed immediately cyclized to a phenanthrene or a spiro-indan. Using 85% sulfuric acid as the dehydrating agent in our work, the olefins which might be expected are shown on the Flow Sheet as (II), (III) and (IV), the cyclized products as (V), (VI) and (VII), the dehydrogenated phenanthrenes as (VIII) and (IX), and the oxidation product of the spiro-indan as (X).

FLOW SHEET



The crude product obtained by the action of 85% sulfuric acid upon the methylcyclohexanol (I) gave no tests for the presence of olefins, and evidently consisted of a mixture of their cyclization products, as shown by a careful distillation under diminished pressure, which yielded a series of fractions differing in boiling point and in refractive index.

Dehydrogenation of this mixture of cyclization products, by fusion with selenium, yielded 2-methylphenanthrene (IX) as the chief product, thus indicating the probable antecedent formation of the octahydro derivative (VI) and of its predecessor the β-phenylethyl-3-methylcyclohexene-6 (III).

When the cyclization mixture was subjected to oxidation with chromic oxide in glacial acetic acid solution, or especially if using the lower-boiling portion of it, the methyloctahydrophenanthrene was burned up, and there was isolated a small amount of the α-3-methylcyclohexylhomophthalic acid (X), which probably owed its origin to the spirane (VII), the progenitor of which must have been either (III) or (IV). In view of our earlier experiments,[2] it seems unlikely that the spirane underwent any rearrangement to the 2-methylphenanthrene during the selenium dehydrogenation.

The dehydration of the cyclohexanol (I) by 85% sulfuric acid, therefore, as carried out by us, gave mainly the olefin (III), possibly with small quantities of (IV), as the first step in the reaction, and these then rearranged promptly to the isomeric phenanthrene (VI) and spirane (VII) derivatives. This is in agreement with our previous work.[3]

No trace of 4-methylphenanthrene (VIII) was detected, nor any of the 1-methyl isomer, which

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[1] Wallach, *Ann.*, **395**, 83 (1913); **396**, 271 (1913); see also Signaigo and Cramer, THIS JOURNAL, **55**, 3326 (1933).

[2] Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 300 (1936).

[3] Perlman, Davidson and Bogert, *ibid.*, **1**, 288 (1936).