CONVERSION OF (α'-BENZYLIDENE-α-CYCLOHEXANONYL) (α-CYCLOHEXANONYL)PHENYLMETHANE TO HYDROACRIDINES*

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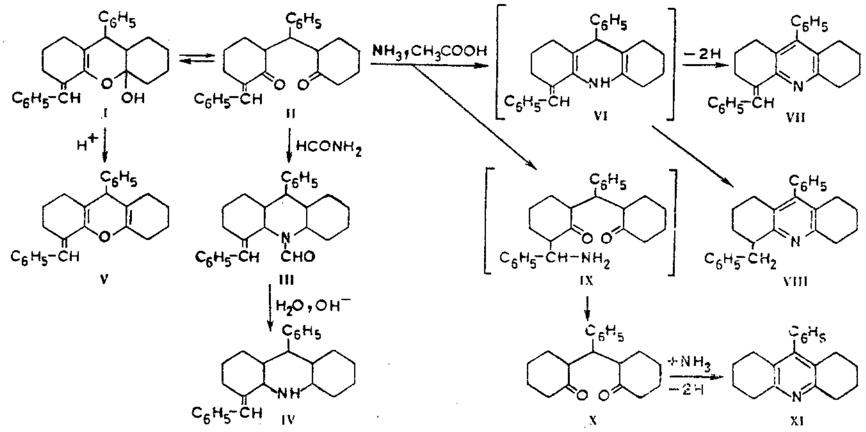
9-Phenyl-5-benzylidene-1,2,3,4,4a,5,6,7,8,9a-decahydro-4a-xanthenol, which exists in solution in equilibrium with (α'-benzylidene-α-cyclohexanonyl) (α-cyclohexanonyl)phenylmethane, forms the corresponding perhydroacridine under the conditions of the Leuckart reaction and reacts with ammonium acetate to give a mixture of compounds of the sym-octahydroacridine series. Dehydration occurs simultaneously in both cases, and 9-phenyl-4-benzylideneoctahydroxanthene is formed.

We recently established that the previously described [2] 1,5-diketone II has hydroxyhydroxanthene structure I in the crystalline form [3] and that these two compounds are in equilibrium in solution. This compelled us to make a more detailed examination of the previously described [4, 5] conversions from II to hydroacridine systems.

Under the conditions of the Leuckart reaction, I forms octahydroxanthene V and formylhydroacridine III. The IR spectrum of the latter contains absorption bands at 2720 (C−H bond in aldehydes) and 1650 cm^{-1} (amide carbonyl group). Formyl derivative III is hydrolyzed to the known perhydroacridine IV.



The reaction of I with ammonium acetate in acetic acid proceeds in a more complex manner. It has been reported [5] that two isomeric 4-benzylidine-9-phenyl-sym-octahydroacridines (VII) were obtained as a result of this reaction. We isolated octahydroxanthene V and three nitrogen-containing substances from the reaction mixture. Of these three substances, the first corresponded to one of the isomers of VII previously described in [5], the second substance was 9-phenyl-4-benzyl-sym-octahydroacridine (VIII), which was evidently assumed to be a second isomer of VII in [5], and the third substance was found to be the known [6] 9-phenyloctahydroacridine (XI). The VIII structure was confirmed by the PMR spectrum (doublet of benzyl protons at δ 3.52 ppm, J = 11 Hz), the mass spectrum (molecular ion with m/e 353 and an ion with m/e 262 corresponding to the

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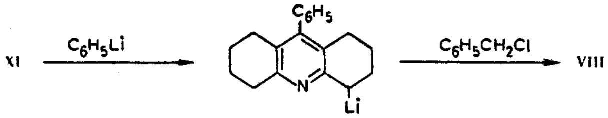
loss of a benzyl group), and by alternative synthesis, for which hydroacridine XI was treated with phenyllithium, and the resulting 9-phenyl-4-octahydroacridinyllithium (XII) was treated with benzyl chloride.



XII

The formation of VII-XI can be represented in the following way. Diketone II reacts with ammonia to give hydroacridine VI and amino diketone IX. Hydroacridine VI is stabilized by conversion to VII and VIII. Amino diketone IX, being a Mannich base, undergoes deaminoalkylation [7] to give diketone X. The latter is converted to hydroacridine XI via a known scheme [6]. Octahydroxanthene V is apparently formed in both reactions through dehydration of decahydroxanthenol I.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were recorded with a ZKR-60 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer at 70 eV. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The compounds were identified in all cases by means of mixed-melting-point determinations with authentic samples.

10-Formyl-9-phenyl-4-benzylideneperhydroacridine (III). A mixture of 12.0 g (0.032 mole) of I, 12 ml of formamide, and 6 ml of 85% formic acid was refluxed for 2 h. When the mixture was cooled, it solidified to a crystalline mass. This mass was washed on a filter with water, dried, and extracted with four 150-ml portions of boiling hexane. The extract was evaporated to give 3.4 g (29.5%) of 9-phenyl-4-benzylidine-sym-octahydroxanthene (V) with mp 110-112° [from dimethylformamide (DMF)] (mp 111° [3]). The hexane-insoluble crystals [7.55 g (61%)] were found to be III with mp 225° (dec., from alcohol). Found: N 4.4%. $C_{27}H_{31}NO$. Calculated: N 3.6%.

9-Phenyl-4-benzylideneperhydroacridine (IV). A solution of 1.64 g of formyl derivative III in 32 ml of a 1 N alcohol solution of sodium hydroxide was refluxed for 2 h, after which it was cooled, and the precipitated crystals were washed with alcohol and dried to give 1.25 g (82%) of a product with mp 126-128° (from alcohol) (mp 124-126° [4]). PMR spectrum: δ 6.70 ppm (singlet, olefinic proton).

Reaction of Ammonium Acetate with 9-Phenyl-5-benzylidene-1,2,3,4,4a,5,6,7,8,9a-decahydro-4a-xanthenol (I). A mixture of 4.25 g (0.01 mole) of I, 10 g (0.13 mole) of ammonium acetate, and 40 ml of acetic acid was refluxed for 1.5 h, after which it was cooled and made alkaline to pH 8 with saturated sodium carbonate solution. The resulting precipitate was removed by filtration, washed with water, dried, and treated with a mixture of 40 ml of ether and 60 ml of dilute HCl solution (1 : 1). The ether layer was separated and filtered through 5 g of aluminum oxide. The filtrate was evaporated to give 0.67 g (16.6%) of V with mp 111-113° (from alcohol). The hydrochloric acid layer was diluted to twice its volume with water and extracted with chloroform. The extract was washed with water, dried with magnesium sulfate, and evaporated. The residue (2.93 g), which was a vitreous dark-brown mass, was separated into its components by means of preparative thin-layer chromatography (TLC) on activity II aluminum oxide with hexane–ethyl acetate (40 : 1). Approximately 500 mg of the mixture was applied to each 24 × 36 cm plate. The entire mixture was separated in six stages to give the following compounds. The separation gave 0.715 g (17.9%) of 9-phenyl-4-benzylidene-sym-octahydroacridine (VII) with R_f 0.78 and mp 171-172° (from dioxane–alcohol) (mp 172.5° [5]). The separation also gave 0.77 g (19.1%) of 9-phenyl-4-benzyl-sym-octahydroacridine (VIII) with R_f 0.32 and mp 141-143° (from hexane). Found: C 88.3; H 7.9; N 4.3%. $C_{26}H_{27}N$. Calculated: C 88.3; H 7.7; N 4.0%. The separation also yielded 0.39 g (13.1%) of 9-phenyl-sym-octahydroacridine (XI) with R_f 0.2 and mp 178-179° (mp 177-178° [6]).

9-Phenyl-4-benzyl-sym-octahydroacridine (VIII). A total of 50 ml of a 0.8 M solution of phenyllithium in ether [8] was added with stirring in an argon atmosphere to 5 g (0.02 mole) of 9-phenyloctahydroacridine XI [6] in 50 ml of absolute ether, and the mixture was allowed to stand for 20 h. A solution of 5.1 g (0.04 mole) of benzyl chloride in 10 ml of ether was then added to the bright-red solution, and the mixture was stirred at room temperature for 2 h. It was then treated successively with 5 ml of water and 50 ml of 20% hydrochloric acid, and the liberated oil was separated and shaken with a mixture of 100 ml of benzene and 50 ml of 30% sodium hydroxide solution. The benzene layer was separated and evaporated to give 4.8 g (71%) of VIII with mp 140-142° (from hexane).

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CARBOLINES

VIII.* α-CARBOLINE COMPOUNDS FROM β-(3-INDOLYL) KETONE OXIMES

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Anhydronium bases of 2-chloro-α-carbolines and 3,4-dihydro-β-carbolines are formed by Beckmann rearrangement of β-(3-indolyl) ketone oximes. In a number of cases the formation of anhydronium bases becomes the predominant process.

Using previously developed methods [2, 3] we have synthesized new substituted β-carbolines XIV-XVI, which are potential physiologically active compounds. Ethylidene- and isobutylideneacetones reacted with indole under the influence of perchloric acid to give indolyl ketones I and III, which were converted to oximes II and IV (for the synthesis of α-substituted oxime VI, tert-butyl α-propylacetoacetate was alkylated with gramine methylsulfate). Oximes II, IV, and VI were converted to 3,4-dihydro-β-carbolines by 1-min contact with phosphorous pentachloride in warm nitrobenzene. The resulting hydrochlorides of X-XIII were dehydrogenated by heating in glycol with palladium black prepared by the method in [4].

In the reaction of oxime II with PCl_5, a considerable amount of a yellow substance that forms a hydrochloride that is difficult to dissolve in water was isolated along with carboline X. According to the mass-spectrometric data and the results of elementary analysis the base corresponding to this hydrochloride had the empirical formula $C_{13}H_{11}ClN_2$. Absorption characteristic for the NH bond in indole was not observed in its IR spectrum. The PMR spectrum contained a multiplet at 7.20-8.00 ppm, singlets of two methyl groups at 4.17 and 2.55 ppm, and a one-proton singlet at 6.52 ppm. From these data we proposed the 1H-1,4-dimethyl-2-chloro-α-carboline structure (XVII) for the isolated substance. The position of the chlorine atom was confirmed by the following data: The product of reductive dechlorination (XVIII) had a PMR spectrum in which the H_a proton appeared as a doublet at 6.67 ppm ($J = 6.5$ Hz) and a new (as compared with XVII) one-proton doublet appeared at 8.16 ppm ($J = 6.5$ Hz). The magnitude of the chemical shift and the spin–spin splitting constant indicate that the H_b proton that replaced the chlorine atom occupied an adjacent position with respect to the nitrogen atom and H_a.

The synthesis of the known 1H-1-methyl-α-carboline (XXIV) [5] by the action of phosphorus pentachloride on oxime VII [6] served as another confirmation of the correctness of formulas XVII and XVIII. α-Isocarboline XXIV and its ethiodide (XXVIII) had physical constants in agreement with the literature data [5].

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*See [1] for communication VII.

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