

HYDANTOINS, THIOHYDANTOINS AND GLYCOCYAMIDINES XX*

SYNTHESIS AND CONDENSATION OF 4'-NITRO-4-METHOXY-BENZIL WITH
BENZYL-GUANIDINE

By

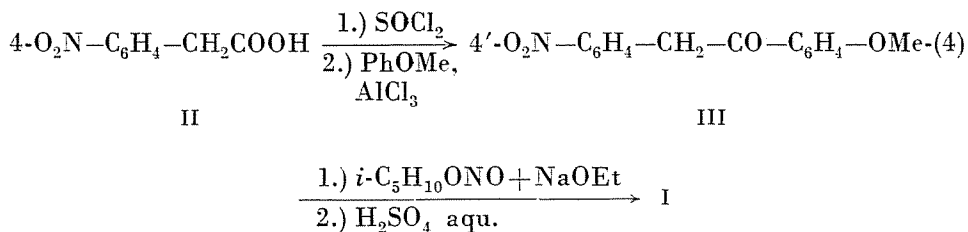
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(Received March 20, 1964)

During an investigation of the condensation of monosubstituted guanidines with benzil leading *inter al.* to substituted glycoeyamidines some striking orientation phenomena have recently been observed and interpreted in terms of a mechanism suggested by us [1]. For testing the correctness of this mechanism it was found to be desirable to extend the reaction to asymmetrically substituted benzils with carbonyl groups which, as a result of the presence of unequal substituents attached to the two benzene rings, differ considerably in electrophilic reactivity; and, at the same time, to investigate the reaction with the aid of the tracer technique. Since we considered 4'-nitro-4-methoxy-benzil (I) as a suitable model for this task, a method, capable of being applied also for the synthesis of I labeled with ^{14}C in *one* of its carbonyl groups, was elaborated. In addition, we investigated the condensation of I with benzyl-guanidine under different conditions.

I had been synthesised by Japanese workers according to the following scheme [2]:

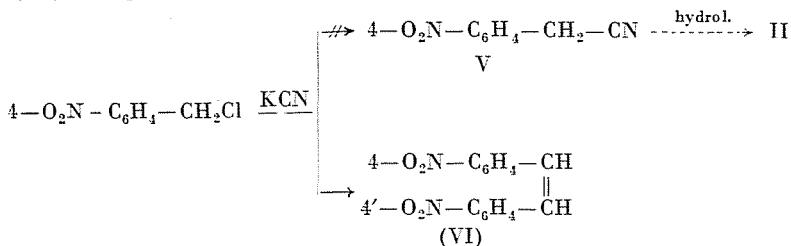


Yields have not been stated (at least in the abstract of the paper); in our hands, however, the yields of the two separate steps proved to be of the order of 60 and 50%, respectively. The yield in the second step could be considerably raised (to 85–90%) by performing this step through direct oxidation by selenium dioxide in the presence of acetic anhydride.**

* For part XIX see K. LEMPERT et al.: Tetrahedron Letters 1964, No. 38, p. 2679.

** For analogous oxidations of desoxy-benzoins cf. eg. [3].

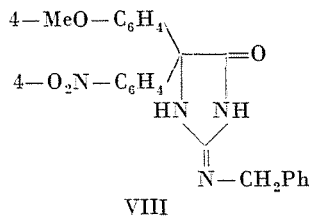
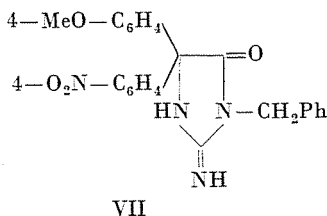
As to the preparation of II, in view of the need of a method suitable also for the synthesis of I labeled with ^{14}C in one of its carbonyl groups, p-nitro-benzyl chloride (IV) was the obvious starting material. IV, on being treated with potassium cyanide, however, did not yield V but, instead, 4,4'-dinitro-stilbene (VI), cf. [4a]:



The reaction is thus analogous to the reaction of IV with potassium hydroxide,* the potassium cyanide in our case simply playing the role of a dehydrochlorinating base. Attempts to prepare V from IV by replacing the potassium cyanide with the non-basic silver or copper(I) cyanide failed.

Thus II had to be prepared from benzyl chloride by first transforming it into the nitrile and subsequently nitrating and hydrolysing the latter. The overall yield in this series did not prove to be satisfying, mainly because the nitration step at best gives only 50% of the p-isomer.

Condensation of 4'-nitro-4-methoxy-benzil (I) with benzyl-guanidine in a weakly basic medium, that is, in the presence of triethylamine yielded, analogously to the previously described condensation of unsubstituted benzil [1a], however only in a low yield, 3-benzyl-5-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-glycoeyamidine(VII), its structure assignment being based on analogy, which could not be directly crystallized, only after purification through its oxalate. Since the solubility of I in alcohols proved, in contrast to that of the unsubstituted parent compound, to be very low, the reaction had to be performed in considerably dilute solution.



In one case very small amounts of isomeric VIII could be isolated as a by-product.

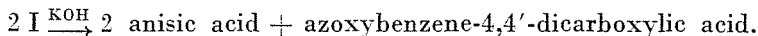
By performing the same condensation in a more basic medium, i.e. in the presence of potassium hydroxide (molar ratio: I: benzyl-guanidine:

* For the mechanism of this reaction see [4b].

:KOH = 1 : 1.5 : 0.75), VIII became the chief product, its yield, however, being only mediocre. It was hoped that the yield could be raised by using larger amounts (5.5 moles) of potassium hydroxide; the only product which could be isolated under these conditions was, however, a nitrogen free acidic substance of mp. 183°, which later proved to be identical with anisic acid.

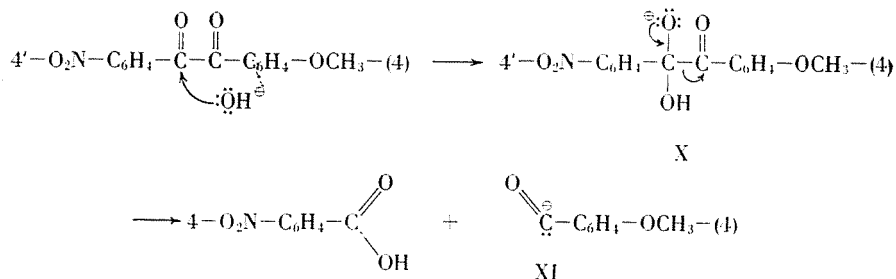
The same substance was formed when it was attempted to achieve a simple benzylic acid rearrangement of I by treating it with alcoholic potassium hydroxide. Accordingly, we have to deal with two concurring reactions when treating I with benzyl-guanidine and potassium hydroxide, one being favoured by high alkalinity of the medium and leading to anisic acid, and the other to VIII.

Hereupon there arose the question as to the fate of the p-nitro-benzoyl part of I in the course of the first reaction. By repeating thoroughly the reaction of I with potassium hydroxide either in the presence or in the absence of benzyl-guanidine a further acidic substance could be isolated which, by mp., IR and UV spectrum proved to be identical with azoxy-benzene-4,4'-dicarboxylic acid (IX) the stoichiometry of the reaction being



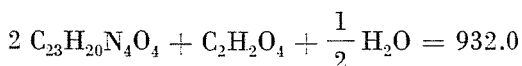
A somewhat similar cleavage of a benzil under benzylic acid rearrangement conditions has already been described by ZININ [5], who stated that 4-nitro-benzil becomes cleaved by heating with alcoholic potassium hydroxide to azobenzene-4,4'-dicarboxylic acid and "hydroxy-benzoic acid", the latter being not characterized further.*

The cleavage of I with potassium hydroxide is obviously initiated by the nucleophilic attack of a hydroxyl anion on the carbonyl carbon α to the nitro-phenyl group. In contrast to a benzylic acid rearrangement, however, this is not followed by a 1 : 2 shift of the 4-nitro-phenyl group within the adduct X but, instead, by the splitting off of the 4-anisoyl group in form of the corresponding anion (XI). One might assume that in the alkaline solution



* Added in proof: This reaction has been reinvestigated later by M. L. BLACK and H. A. SMITH [7] who found that the structure assignments made by ZININ were incorrect, the products formed being in reality benzoic acid and azoxy-benzene-4,4'-dicarboxylic acid.

suddenly deepened. After refluxing for 4 hours the mixture was evaporated to dryness and the residue of viscous orange oil shaken simultaneously with 30 ml each of benzene and water, the latter containing 0.56 g (10 mmoles) of potassium hydroxide, until total dissolution was achieved. The aqueous layer was twice extracted with 10 ml portions of benzene, the combined benzene solutions dried over MgSO_4 and subsequently evaporated again. The residual orange gum was treated after dissolving it by slight heating in 10 ml acetone with a solution of 0.75 g (6 mmoles) of oxalic acid dihydrate in 5 ml of acetone, whereby a yellowish crystalline precipitate on cooling deposited which was collected and washed with acetone. Yield: 1.5 g (58%) of the neutral oxalate hemihydrate $\left(\text{B}_2 \cdot (\text{COOH})_2 \cdot \frac{1}{2} \text{H}_2\text{O}\right)$, mp. after crystallisation from dimethylsulfoxide—methanol (85% recovery): 237—8° (dec.).

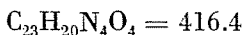


Calc'd: C: 61.86 H: 4.65 N: 12.03

Found: C: 61.78 H: 4.71 N: 12.04
62.09 4.44 11.91

In another experiment in which ethanol was used as solvent, approximately the same amount of crude oxalate was isolated and, in addition, 0.05 g (2.2%) of isomeric VIII (see later) in form of the free base, mp.: 244—5° (from dimethylformamide), which separated from the original reaction mixture on cooling.

0.93 g (1 mmole) of the crude oxalate of VII were refluxed for 10 minutes with a solution of 0.14 g (2.5 mmoles) of potassium hydroxide in a mixture of 0.5 ml of water and 1 ml of alcohol. The reddish gummy precipitate on standing overnight solidified and could be recrystallized from 2 ml of toluene. Yield: 0.29 g (35%) of a yellowish crystalline powder, mp., after recrystallisation: 168—169°C.



Calc'd: C: 66.33 H: 4.84 N: 13.46

Found: C: 66.37 H: 4.93 N: 13.40

*N*²-Benzyl-5-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-glycoyamidine (VIII)

1.55 g (8.33 mmoles) of benzyl-guanidinium chloride and 1.58 g (5.55 mmoles) of I were dissolved by refluxing in 120 ml isopropyl alcohol. On the subsequent addition of a solution of 0.70 g (12.5 mmoles) of potassium hydroxide in 2 ml of water a precipitate was instantaneously formed which did not disappear even on refluxing for 6 hours. After standing overnight the precipitate was filtered and subsequently washed with methanol and water. Yield:

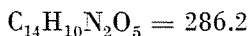
0.65 g (28%) VIII, after two crystallizations from DMF yellowish needles, mp.: 245–7° (dec.).



Calc'd: C: 66.33 H: 4.84 N: 13.46

Found: C: 66.09 H: 4.96 N: 13.80
 66.66 5.02 13.61

By evaporating the alkaline mother liquor to dryness, extracting the gummy brown residue with benzene, chloroform and aqueous alcohol, dissolving the combined residues of the benzene and chloroform extract in acetone and acidifying with oxalic acid 0.53 g (63%) anisic acid, identified by mp. and analysis, as well as an additional amount of 0.11 g (4.7%) VIII and, by acidifying the aqueous alcoholic extract with hydrochloric acid, a slight amount of azoxy-benzene-4,4'-dicarboxylic acid (IX) could be isolated too. This latter was identified by analysis and UV spectrum.



Calc'd: C: 58.74 H: 3.52 N: 9.79

Found: C: 58.73 H: 3.72 N: 9.83

UV spectrum in 0.1 n NaOH solution:

λ_{\max} = 265.5 m μ ,	ϵ = 10.5 · 10 ³ and
333 m μ ,	ϵ = 17.4 · 10 ³ ,
lit. [6]: 268 m μ ,	ϵ = 11.7 · 10 ³ and
334 m μ ,	ϵ = 18.4 · 10 ³

Variation of the amount of the condensation agent

By repeating the above experiment in alcoholic solution and using various amounts of potassium hydroxide, the following results were obtained:

KOH, mmoles	Isolated products		
	VIII	anisic acid	IX
37.5	0	0.67 g = 80%	0.52 g = 66%
12.5	0.60 g = 26%	sum: 0.46 g	
11.1	0.75 g = 32%	sum: 0.17 g	
9.7	0.70 g = 30%	sum: 0.10 g	

The glycoeyamidine (VIII) was separated from the acidic materials by alkaline extraction of the latters from the crude product.

Attempted benzilic acid rearrangement of I.

A mixture of 2.85 g (10 mmoles) of I, 4.20 g (75 mmoles) of potassium hydroxide and 8.4 ml each of water and ethanol was heated to 60° for 6 hours. The resulting mixture was worked up in two ways:

a) By acidifying the clear solution obtained by filtration of the dark mixture with hydrochloric acid 1.05 g (69%) anisic acid were obtained, mp. after recrystallisation from benzene: 183°, lit: same, colourless crystals.

$$C_8H_8O_3 = 152.1$$

Calc'd: C: 63.15 H: 5.30

Found: C: 63.03 H: 5.36

b) By diluting with 100 ml water until a practically complete dissolution of the precipitate and acidifying the filtered solution with 20 ml conc'd hydrochloric acid, 2.70 g of a creme coloured microcrystalline powder was obtained. From this, by twice extracting with 20 ml portions of ethanol 1.23 g (81%) anisic acid could be removed. The residual 1.47 g (100%) of crude IX was subsequently freed from anorganic salts by extracting with hot water and subsequently recrystallized from DMF.

Attempted reaction of anisaldehyde with p-nitro-benzoic acid

10 mmoles each of anisaldehyde and p-nitrobenzoic acid were refluxed with 20 mmoles of potassium hydroxide for 9 hours in aqueous dioxane. By working up the reaction mixture only anisaldehyde (51%) and p-nitrobenzoic acid (72%) could be recovered.

Cannizzaro reaction of anisaldehyde

By treating anisaldehyde with aqueous alcoholic potassium hydroxide for 5 hours at 60°, that is, under conditions applied during the synthesis of VIII (see above), 26, 26.5 and 30% of the anisaldehyde used could be recovered as anisic acid, anisalcohol and anisaldehyde, respectively, the latter two being identified as the phenyl-urethane and the dinitrophenylhydrazone, respectively.

Acknowledgement : Thanks from the authors are due to Mrs. Ilona Balogh-Batta and Dr. László Láng for performing the microanalyses and the UV spectra, respectively.

Summary

The reaction of 4'-nitro-4-methoxy-benzil (I) with benzyl-guanidine in the presence of basic condensation agents was investigated, the chief reaction products being, in the order of increasing basicity of the medium 3-benzyl- (VII), N²-benzyl-5-(4-nitro-phenyl)-5-(4-methoxy-phenyl)-glycoeyamidine (VIII) and anisic + azoxy-benzene-4,4'-dicarboxylic acid (IX), respectively. The two latter products are also formed from I under simple benzilic acid rearrangement conditions.

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