BENZOXAZINES AND RELATED COMPOUNDS

IV.* NITRATION OF 2-SUBSTITUTED 4,4-DIETHYL-4H-1,3-BENZOXAZINES

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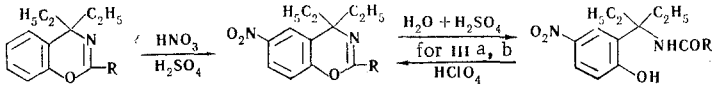
The action of a nitrating mixture on 2-substituted 4,4-diethyl-4H-1,3-benzoxazines gives the corresponding 6-nitro derivatives, which can be isolated as such or as the hydrolysis products – N-acyl-α,α-diethyl-2-hydroxy-5-nitrobenzylamines. The latter cyclize to the corresponding 4H-1,3-benzoxazines under the influence of perchloric acid.

The previously obtained [1-3] 4,4-dialkyl-4H-1,3-benzoxazines are of interest as objects for the investigation of the chemical and physicochemical properties of such compounds and for the search for pharmacologically active compounds.

As a prime example of the study of the action of electrophilic reagents on this system, we selected the nitration of Ia-c. It is difficult to predict which position the nitro group will enter, particularly if one considers that the indicated benzoxazines form salts in acidic media through protonation of the basic nitrogen atom (pK_a for Ia in 50% alcohol at 20°C is 3.92†). The use of acetyl nitrate (obtained in situ by the reaction of cupric acetate with nitric acid and acetic anhydride in acetic acid) excluded the use of a mineral acid medium but, unfortunately, did not give positive results.



Ia-c IIa, b IIIa-c

a R=CH3; b R=CH2Cl; c R=C(OH)(CH3)2

The nitration of Ia, b in concentrated H_2SO_4 solution with nitric acid (sp. gr. 1.52) proceeds comparatively readily. (It is practically complete in 2 h, as one can judge from the PMR spectra of the reaction mixture; the PMR spectra of a concentrated H_2SO_4 solution of genuine IIa and the starting Ia were recorded for comparison.) In order to ensure that the benzoxazine ring of the resulting nitro derivatives (IIa, b) is retained during treatment of the reaction mixture, the sulfuric acid solution must be poured gradually into excess aqueous alkali. If, however, the reaction mixture is poured into water (containing ice), the products of the hydrolytic cleavage of the benzoxazine ring – N-acyl-α,α-diethyl-2-hydroxy-5-nitrobenzylamines (IIIa-c) – are obtained. Hydroxyamides IIIa, b cyclize quite smoothly to IIa, b via the method proposed in [1] – treatment with 69-70% perchloric acid in acetonitrile. This route to the synthesis of II is possibly less convenient than the first route, particularly when it is necessary to use large amounts of materials. An oily substance was isolated from the cyclization of IIIc. (No attempt was made to obtain it in the pure state.)

Nitrobenzoxazines IIa, b are light-yellow, relatively low-melting substances. The position of the nitro group in II was established by spectral methods. The PMR spectrum of IIa indicates that the nitro group is

*See [1] for communication III.

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in the 6 or 7 position, since there is a doublet with an intensity of one proton unit and J = 8.5 Hz at 6.9 ppm; a second signal with a chemical shift of 7.9 ppm in the form of a doublet of doublets (J_{ortho} = 8.5, J_{meta} = 2.5 Hz) is caused by the proton in the ortho position relative to the first "isolated" proton and in the meta position relative to the third "isolated" proton, the signal of which at 7.8 ppm is overlapped with the strong-field components of the doublet of doublets. The PMR spectra of III are also in agreement with this conclusion. The IR spectrum* of IIIa (in acetonitrile) contains rather intense absorption bands at 832 and 892 cm^{-1}, which indicates 1,2,4-substitution in the benzene ring [4]. (There is a series of bands, the assignment of which is difficult, in the spectrum of IIa in this region.) The frequency of the symmetrical stretching vibration (ν_S) of the nitro group of IIIa is 1341 cm^{-1} and corresponds to ν_S of the nitro group in compounds of the 4-nitroanisole type; it is considerably lower than the value for the corresponding substituted benzenes with a meta orientation of the nitro group [5]. The UV spectrum of IIIa serves as an additional and sufficiently reliable confirmation of the fact that it contains a 4-nitrophenol fragment. There is a strong absorption band at 320 nm (log ε 4.00) in the spectrum of an alcohol solution of IIIa. The same absorption at this region is also observed for 4-nitrophenol, while the long-wave absorption maxima of 3-nitrophenol are less intense (λ_{max} 332 nm, log ε 3.39) [6]. A comparison of the spectra of 3-nitrophenol, 4-nitrophenol, and IIIa in alkaline solutions is particularly demonstrative: λ_{max}, nm (log ε): 393 (3.18), 399 (4.29), and 4.0 (4.38), respectively. The nitro group in II is consequently in the 6 position. We note that we were unable to accomplish the nitration of N-acetyl-α,α-diethyl-2-hydroxybenzylamine because of resinification.

Thus, as a result of the action of a nitrating mixture on 4,4-dialkyl-4H-1,3-benzoxazines, we were able to synthesize not only the corresponding 6-nitrobenzoxazines but also compounds of nonbasic character of the III type, which contain p-nitrophenol and amide groupings; this may be used for a qualitative analysis of the indicated benzoxazines and further syntheses in this series.

EXPERIMENTAL

The UV spectra were recorded with an SF-4 spectrophotometer, the IR spectra were recorded with a DS-301 spectrophotometer, and the PMR spectra were recorded with RS-60 and Varian T-60 (for IIa) spectrometers with operating frequencies of 60 MHz.

N-Acetyl-α,α-diethyl-2-hydroxy-5-nitrobenzylamine (IIIa). A 1-ml sample of HNO_3 (sp. gr. 1.52) was added dropwise to a cooled solution of 3.0 g of Ia [3] in 30-40 ml of concentrated H_2SO_4. The mixture was allowed to stand for 48 h and poured over ice. The resulting mixture was made alkaline with $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate solution was washed with water and vacuum-distilled to give 2.1 g (54%) of IIIa with mp 173-174° C (from nitromethane). Found: C 58.8; H 6.8; N 10.7%. $C_{13}H_{18}N_2O_4$. Calculated: C 58.6; H 6.8; N 10.5%. IR spectrum (KBr pellet), cm^{-1}: 2400-3600 (broad band, associated OH and NH groups), 1647 (amide I), 1550, 1525 (amide II and ν_{as} NO_2), 1334 (ν_S NO_2). PMR spectrum (in CD_3OD), ppm†: 0.7 (t, J = 7.5 Hz, $2CH_3$ in the CH_2CH_3 groups), 2.0 (s, $COCH_3$), 2.2 (q, J = 7.5 Hz, $2CH_2$ in the CH_2CH_3 groups), 6.8 (d, J = 8.6 Hz, 3-H), 8.0 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.8 Hz, 4-H), and 8.0 (d, J = 2.8 Hz, 6-H).

N-Chloroacetyl-α,α-diethyl-2-hydroxy-5-nitrobenzylamine (IIIb). The nitration of 4.8 g of Ib [2] by 1.6 ml of HNO_3 in 38 ml of concentrated H_2SO_4 similarly gave 4.3 g (72%) of IIIb with mp 165-166° C (from ethyl acetate). Found: C 52.0; H 5.7; Cl 11.7; N 9.3%. $C_{13}H_{17}ClN_2O_4$. Calculated: C 51.9; H 5.7; Cl 11.8; N 9.3%. PMR spectrum (in CD_3OD), ppm: 0.8 (t, J = 7.5 Hz, $2CH_3$), 2.3 (q, J = 7.5 Hz, $2CH_2$ in CH_2CH_3), 3.9 (s, CH_2-Cl), 6.7 (d, J = 8.5 Hz, 3-H), 7.8 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.5 Hz, 4-H), 8.0 (d, J = 2.5 Hz, 6-H).

N-(2'-Hydroxy-2'-methylpropionyl-α,α-diethyl-2-hydroxy-5-nitrobenzylamine (IIIc). Similarly, 4.8 g of Ic [2], 1.6 ml of HNO_3, and 38 ml of concentrated H_2SO_4 gave 5.0 g (83%) of IIIc with mp 195-196° C (from nitromethane). Found: C 58.3; H 7.2; N 8.8%. $C_{15}H_{22}N_2O_5$. Calculated: C 58.1; H 7.2; N 9.0%.

2-Methyl-4,4-diethyl-6-nitro-4H-1,3-benzoxazine (IIa). A) A total of 5 ml of 69-70% $HClO_4$ was added dropwise to a solution of 5.0 g of IIIa in 12 ml of acetonitrile in such a way that the temperature of the reaction mixture was 35-40° C. After 48 h, the mixture was poured over ice, and the aqueous mixture was made alkaline with ammonia and extracted with ether. The ether extract was washed thoroughly with 10% KOH and dried with magnesium sulfate. The ether was removed by distillation, and the residue was purified by chromatography with a column packed with activity IV Al_2O_3 with elution by benzene–ether (1 : 1) to give

* The authors thank B. V. Lopatin for recording and interpreting the IR spectra.

† The chemical shifts here and below are given on the δ scale. The abbreviations used are as follows: s is singlet, d is doublet, t is triplet, q is quartet, and dd is doublet of doublets.

2.95 g (63%) of a product with mp 88-89° C. Found: C 62.8; H 6.6; N 11.3%. $C_{13}H_{16}N_2O_3$. Calculated: C 62.9; H 6.5; N 11.3%. IR spectrum (in $CHCl_3$, c 0.13 M, d 0.174 mm), cm^{-1}: 1712 (C=N), 1622, 1588 (benzene ring), 1525 and 1345 (NO_2), PMR spectrum (in $CDCl_3$), ppm: 0.7 (t, J=7.5 Hz, $2CH_3$ in CH_2CH_3), 1.8 (q, J=7.5 Hz, $2CH_2$), 6.9 (d, J=8.5 Hz, 8-H), 7.7-8.3 (5-H and 7-H).

B) A 1-ml sample of HNO_3 (sp. gr. 1.52) was added to a cooled solution of 3.0 g of Ia in 20 ml of concentrated H_2SO_4, and the mixture was allowed to stand for 48 h. It was then added gradually to 45 g of NaOH in 200 ml of water and 200 g of ice and extracted with ether. The ether solution was dried with $MgSO_4$, the ether was removed by distillation, and the residue was chromatographed on activity IV Al_2O_3 with elution by ether–benzene (1:1) to give 2.85 g (78%) of IIa with mp 88-89° C.

2-Chloromethyl-4,4-diethyl-6-nitro-4H-1,3-benzoxazine (IIb). A) As in the preparation of IIa by method A, 2.2 g of IIIb in 10 ml of acetonitrile and 4 ml of $HClO_4$ gave 1.5 g (73%) of IIb with mp 71-72°. Found: C 55.5; H 5.6; Cl 12.3; N 9.8%. $C_{13}H_{15}ClN_2O_3$. Calculated: C 55.2; H 5.4; Cl 12.6; N 9.9%. IR spectrum (in $CHCl_3$, c 0.1 M), cm^{-1}: 1705 (C=N); 1622, 1588 (benzene ring); 1528 and 1345 (NO_2).

B) As in the preparation of IIa by method B, 4.8 g of Ib in 16 ml of concentrated H_2SO_4 and 1.6 ml of HNO_3 gave 2.7 g (44%) of IIb with mp 71-72° C.

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