4-AZAINDANE-1,3-DIONE DERIVATIVES.

II.* SYNTHESIS OF TETRAHYDRO-4-AZABENZ[*f*]INDANE-1,3,8-TRIONES

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UDC 547.836.07:542.953'944'941'938

6,6-Dimethyl-2-methyl(or phenyl)-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-triones were synthesized by reaction of **3-ethoxalyl-5-R-cyclopentane-1,2,4-triones** with 3-amino-5,5-dimethyl-2-cyclohexen-1-one. The products were alkylated, brominated, reduced, and hydrolyzed.

We recently reported a new one-step method for the synthesis of 4-azaindane-1,3-dione derivatives [1] and the tautomeric and prototopic equilibria of these compounds [2]. In the present research we made a more detailed investigation of the reaction of 3-ethoxalyl-5-R-cyclopentane-1,2,4-triones (I) with 3-amino-5,5-dimethyl-2-cyclohexen-1-one (II), which gives 6,6-dimethyl-2-methyl(or phenyl)-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-triones (IIIa, b), the structure of which combines a cyclic β-dicarbonyl grouping and a pyridine ring, as a consequence of which they display properties characteristic for these two systems. Like β-diketones, IIIa are brominated to give VI, the IR spectrum of which (1735, 1765 cm^{-1}) attests to a fixed diketo structure and is similar to the spectra of the previously synthesized 2-nitroso-2,6,6-trimethyl-9-phenyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-trione [3] and 2-halo-substituted 4-azaindane-1,3-diones [4]. Triones IIIa, b react with triethyloxonium fluoroborate to give yellow and bright-red enol ethers VIIa, b. Reduction of IIIa with $Na_2S_2O_4$ gave 1,4-dihydropyridine XI, which is similar to the previously synthesized 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydro-4-azabenz[*f*]indane-1,3,8-trione [3]. This proved the 4-aza structure of products IIIa, b and thereby excludes the possibility of cyclization to give the isomeric 5-azaindane-1,3-dione XII.

Like 2-phenyl-4-azaindane-1,3-diones [4], the tetrahydro-4-azabenz[*f*]indane-1,3,8-triones (IIIa, b) are distinguished by deep coloration in neutral and alkaline media. Their derivative – enol ethers VIIa, b and 2-bromo derivative VI – are less deeply colored.

In this scheme, we arbitrarily depicted IIIa and IIIb in the diketo form, for in the preceding communication the investigated tautomeric and prototropic equilibria of these compounds prove that product IIIa exists as a red anion with a small admixture of betaine Xa in alkaline and neutral solutions. Betaine from Xb predominates for IIIb. In solutions with suppressed ionization (0.1 N HCl) IIIa exists only in yellow enol form IV, which, like IIIa, reacts with N-bromosuccinimide (NBS) to give 2-bromo-2,6,6-trimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-trione (VI). In strongly acidic media IIIa reacts with HCl to form yellow salt IX, which reacts with ammonia to give salt V. The acidity constants [2] were determined, and it was found that $pK_{OH} = 3.32$ for IIIa and 2.39 for IIIb in 50% ethanol. Compounds IIIa, b do not have definite melting points but decompose slowly at 300° C.

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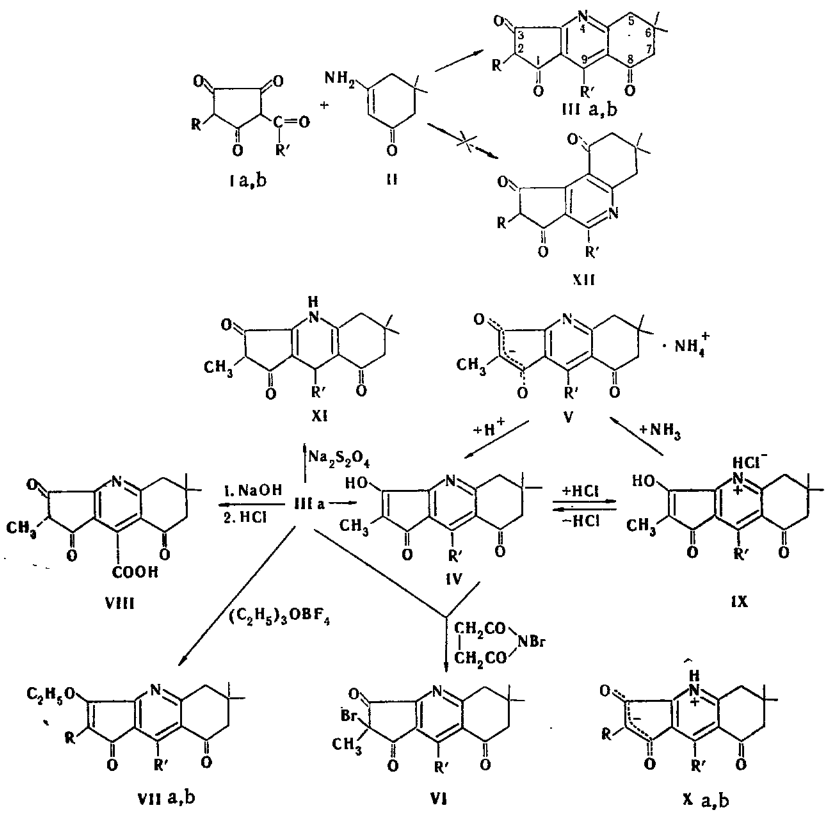
*See [2] for communication I.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 231-234, February, 1975. Original article submitted April 19, 1974.



I, III, VII, X a R = CH_3; b R = C_6H_5, R′ = $COOC_2H_5$

Triones IIIa, b form crystal hydrates with two molecules of water, which are not lost even on prolonged heating in vacuo. The presence of water was also proved by mass spectrometry. The molecular ion of the corresponding compound is equal to the theoretically determined molecular weight, disregarding the two water molecules.

EXPERIMENTAL

The IR spectrum of a dioxane solution of IIIa was recorded with a UR-10 spectrometer, whereas the IR spectra of mineral oil suspensions of all of the remaining compounds were recorded with a UR-20 spectrometer. The UV spectra of aqueous solutions of IIIa, IV, and V and of an alcohol solution of XI were measured with a Specord UV-vis spectrophotometer, and the UV spectra of 50% aqueous alcohol solutions of IIIa, IIIb, VII, and X were recorded with an SFD-2 spectrophotometer. The PMR spectrum was measured with a Perkin–Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. Deuterium oxide was used as the solvent for IIIa. The molecular weights were measured with an MKh-1303 mass spectrometer.

2,6,6-Trimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-trione (IIIa). A mixture of 4.5 g (0.02 mole) of Ia and 2.8 g (0.02 mole) of II was refluxed in 150 ml of absolute ethanol for 3.5 h, after which the ethanol was removed by distillation, and the brown residue was dissolved in a small amount of ethyl acetate and chromatographed with a column (3 × 75 cm) filled with Al_2O_3. The first colored zone was eluted with ethyl acetate (the structure of the product was not established). The second zone was eluted with ethanol. Removal of the solvent by distillation gave 1.8 g (27.3%) of bright-red crystals of IIIa with mp > 250° (dec., ethanol). The product was quite soluble in water but insoluble in nonpolar solvents. IR spectrum, cm^{-1}: 1550, 1595; 1630, 1705, 1730, 3430, 3520, and 3590 (OH). UV spectrum, λ_{max}, nm (log ε): 232 (4.28), 265 (4.18), 362 (3.96), and 472-478 (3.27). PMR spectrum, δ: 2.89 and 2.51 (broad singlets), methylene protons in the 5 and 7 positions; 1.69 (singlet), methyl protons in the 2 position; 1.05, methyl protons in the 6 position, 4.43 and 1.38 ppm (quartet and triplet, respectively), methylene and methyl protons of the ethoxycarbonyl group. Found: C 59.7; H 6.1; N 3.9%; M 329 (mass spectrum). $C_{18}H_{19}NO_5 \cdot 2H_2O$. Calculated: C 59.2; H 6.3; N 3.8%; M 329.4 (without crystallization water).

2,6,6-Trimethyl-3-hydroxy-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]ind-2-ene-1,8-dione Hydrochloride (IX). A 0.37-g (1 mmole) sample of dry IIIa was treated with dry HCl until the bright-red substance was converted to a bright-yellow substance (1-2 min). Workup gave 0.21 g (56.8%) of IX with mp 160-170° (dec., from dry ethyl acetate). IR spectrum, cm^{-1}: 1565, 1610, 1700, 1740, 3330 (OH). UV spectrum, λ_{max}, nm (log ε): 233 (4.46), 265 (3.96), 362 (3.72), 472-476 (3.0). Found: C 59.6; H 5.3; Cl 10.1; N 3.7%; M329 (mass spectrum). $C_{18}H_{19}NO_5 \cdot HCl$. Calculated: C 59.1; H 5.5; Cl 9.7; N 3.8%; M 329.4 (without HCl).

2,6,6-Trimethyl-3-hydroxy-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]ind-2-ene-1,8-dione (IV). A 0.1-g (0.27 mmole) sample of IX was refluxed for 10 min in 20 ml of water, after which the mixture was treated with activated charcoal and filtered. The filtrate was vacuum evaporated to dryness, and the residue was crystallized from ethyl acetate to give 0.02 g (21.1%) of bright-yellow crystals of IV with mp 105-110° (dec.). IR spectrum, cm^{-1}: 1580; 1615; 1695, 1715, 3240, 3335, and 3500. Found: C 62.1; H 6.1; N 3.8%. $C_{18}H_{19}NO_5 \cdot H_2O$. Calculated: C 62.2; H 6.2; N 4.0%.

2,6,6-Trimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]-indane-1,3,8-trione Ammonium Salt (V). A 0.2-g (0.59 mmole) sample of IV was dissolved in 25 ml of dry acetone, the mixture was cooled with cold water, and dry ammonia was bubbled through it for 1-2 min until the yellow solution became bright-red and a red substance began to precipitate. Workup gave 0.16 g (76%) of V with mp 153-155° (acetone). IR spectrum, cm^{-1}: 1569, 1611, 1670, 1721, 1744, and 3230 (OH). UV spectrum, λ_{max}, nm (log ε): 232 (4.46), 265 (3.96), 362 (3.72), and 472-476 (3.00). Found: C 60.6; H 6.4; N 7.5%. $C_{18}H_{22}N_2O_5 \cdot 0.5H_2O$. Calculated: C 60.8; H 6.5; N 7.9%.

2-Bromo-2,6,6-trimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-trione (VI). A 0.23-g (0.13 mmole) sample of NBS was added at room temperature to a suspension of 0.37 g (1 mmole) of IIIa in 10 ml of chloroform, and the flask containing the reaction mixture was shaken for 2-5 min, during which the red suspension was converted to a colorless solution. A white substance began to precipitate in the cold. Workup gave 0.15 g (36.6%) of VI with mp 163-164° (ethanol). The product dissolved in sodium ethoxide to give a dark-brown solution. IR spectrum, cm^{-1}: 1567, 1703, 1735, and 1765. UV spectrum, λ_{max}, nm (log ε) in neutral and acidic ethanol: 233 (4.45) and 305 (3.96); in alkaline ethanol: 220 (4.36), 294 (3.94), and 380 (3.88). Found: C 53.2; H 4.5; Br 19.5; N 3.7%. $C_{18}H_{18}BrNO_5$. Calculated: C 53.2; H 4.4; Br 19.5; N 3.4%. Compound VI was similarly obtained from enol IV.

3-Ethoxy-2,6,6-trimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]ind-2-ene-1,8-dione (VIIa). A 0.38-g (2 mmole) sample of triethyloxonium fluoroborate was added to a suspension of 0.37 g (1 mmole) of IIIa in 25 ml of methylene chloride, and the mixture was heated on a water bath for 15 min. The resulting dark-yellow solution was evaporated to 5 ml, and the condensed solution was chromatographed with a column filled with Al_2O_3. The ethyl acetate eluate was evaporated to dryness to give 0.18 g (50%) of VIIa as fine bright-yellow needles with mp 105-106° (ethanol). The product dissolved in sodium ethoxide to give an orange solution. IR spectrum, cm^{-1}: 1571, 1610, 1694, 1710, and 1746. UV spectrum, λ_{max}, nm (log ε): 231 (4.32), 248-250 (4.28), 326 (3.99), 336 (3.99), and 390-396 (3.08). Found: C 67.6; H 6.8; N 3.8%. $C_{20}H_{23}NO_5$. Calculated: C 67.2; H 6.5; N 3.9%.

2-Phenyl-6,6-dimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[f]indane-1,3,8-trione (IIIb). A mixture of 2.87 g (0.01 mole) of Ib and 1.3 g (0.01 mole) of II was refluxed for 1 h in 75 ml of absolute ethanol, after which the dark-brown reaction mixture was evaporated to dryness, and the residue was dissolved in a small amount of ethyl acetate. The solution was chromatographed with a column filled with Al_2O_3. The structure of the light-colored product obtained in small amounts after elution with ethyl acetate was not established. The second fraction was eluted with ethanol, and the eluate was evaporated to dryness to give 1.2 g (30.7%) of IIIb as a dark-violet substance with mp > 300° (dec., ethanol). The product was insoluble in nonpolar solvents and only slightly soluble in water. IR spectrum, cm^{-1}: 1539, 1595, 1612, 1665, 1676, 1722, 1746, 3475, and 3615 (OH). UV spectrum, λ_{max}, nm (log ε): 233 (4.33), 264 (4.32), 390 (4.21), 506 (3.49). Found: C 64.3 H 5.5; N 3.3%. $C_{23}H_{21}NO_5 \cdot 2H_2O$. Calculated C 64.6; H 5.9;

2-Phenyl-3-ethoxy-6,6-dimethyl-9-ethoxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]ind-2-ene-1,8-dione (VIIb). A 0.3-g (1.6 mmole) sample of triethyloxonium fluoroborate was added to a suspension of 0.35 g (0.82 mmole) of IIIb in 10 ml of methylene chloride, after which the mixture was heated on a water bath for 5 min. The resulting orange-red solution was evaporated to 3 ml, and the condensed solution was chromatographed with a column filled with Al_2O_3. The ethyl acetate eluate was evaporated to 6-8 ml, after which fine bright-red needles precipitated. Workup gave 0.2 g (58.8%) of VIIb with mp 201-203° (ethanol). IR spectrum, cm^{-1}: 1558, 1610, 1699, and 1742. UV spectrum, λ_{max}, nm (log ε): 241 (4.38), 266-268 (4.30), 336-338 (4.11), and 420-424 (3.36). Found: C 71.5; H 6.0; N 3.4%. $C_{25}H_{25}NO_5$. Calculated: C 71.6; H 6.0; N 3.3%.

2,6,6-Trimethyl-9-hydroxycarbonyl-5,6,7,8-tetrahydro-4-azabenz[*f*]indane-1,3,8-trione (VIII). A solution of 0.5 g of NaOH in 15 ml of absolute ethanol was added to a solution of 0.37 g (1 mmole) of IIIa in 10 ml of absolute ethanol, and the mixture was refluxed for 5-10 min until a dark-red precipitate formed. The mixture was neutralized with concentrated HCl, and the resulting NaCl was removed by filtration. The orange filtrate was evaporated to 15 ml and allowed to stand in a refrigerator. Workup gave 0.18 g (56.3 %) of orange crystals of VIII with mp 265-270° (dec., ethanol), which were quite soluble in water. IR spectrum, cm^{-1}: 1580, 1615, 1686, 1705, and 3470. Found: C 59.8; H 5.3; N 4.4 %. $C_{16}H_{15}NO_5 \cdot H_2O$. Calculated: C 60.2; H 5.4; N 4.4 %.

2,6,6-Trimethyl-9-ethoxycarbonyl-4,5,6,7,8,9-hexahydro-4-azabenz[*f*]indane-1,3,8-trione (XI). A solution of 1 g (5.75 mmole) of $Na_2S_2O_4$ in 10 ml of water was added to a solution of 0.5 g (1.37 mmole) of IIIa in 20 ml of water, and the mixture was stirred at room temperature for 2 h until the red solution became yellow. The yellow solution was then stored in a refrigerator for 24 h and extracted with ethyl acetate (five 50-ml portions). The extract was evaporated to 5 ml, and the condensed solution was chromatographed with a column filled with Al_2O_3. The ethyl acetate eluate was evaporated to give 0.1 (22 %) of a yellow substance with mp 183-184° (ethyl acetate-heptane). The product was soluble in polar solvents and dissolved in sodium ethoxide to give a bright-red solution. IR spectrum, cm^{-1}: 1500, 1598, 1630, 1665, 1698, 1743, 3170, and 3235. UV spectrum λ_{max}, nm (log ε), in neutral and acidic solutions in ethanol: 256 (4.3), 272 (3.98), and 392 (3.75); in an alkaline solution in ethanol: 272 (4.33), 305 sh (4.0), and 494 (3.87). Found: C 65.6; H 6.7; N 4.3 %. $C_{18}H_{21}NO_5$. Calculated: C 65.3; H 6.4; N 4.2 %.

We thank Yu. Yu. Popelis for recording the PMR spectra.

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