SYNTHESIS OF 6-HETARYL-SUBSTITUTED AZULENES AND THEIR REACTIONS WITH 2,6-DIPHENYLPYRYLIUM PERCHLORATE

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A method for the synthesis of 4,6,8-trimethyl- and 4,8-dimethyl-6-(2-thienyl, 2-benzothiazolyl)azulenes from 2,6-dimethyl-4-(methyl, 2-thienyl, 2-benzothiazolyl)-pyrylium perchlorates and cyclopentadienyllithium is described. The possibility of direct pyrylation of azulenes with 2,6-diphenylpyrylium perchlorate is demonstrated. Azulenes with a pyrylium ring in the 1 position were synthesized, and their behavior with respect to ammonium acetate was investigated.

Compounds of the azulene series are characterized by various forms of biological activity, viz., antiphlogistic [1], cancerostatic [2], and bacteriostatic [3] activity, and this makes the search for new methods for their synthesis and improvement of the existing methods an urgent task.

The least accessible of the azulene hydrocarbons are the 6-substituted compounds [4-6]. A method for the preparation of 6-thienylazulene on the basis of 2-butoxy-4-(α-thienyl)-Δ^5-dihydropyran, which was proposed by Porshnev and co-workers [7], is well known. The multistep character of the process and the low yields of the desired products made the 6-thienyl-substituted azulene inaccessible from a practical point of view. Having developed convenient methods for the synthesis of 2,6-dialkyl-4-hetarylpyrylium salts and having ascertained that their properties are similar to those of 2,4,6-trialkyl-substituted pyrylium perchlorates in reactions with nucleophiles [8, 9], we therefore synthesized 6-hetaryl-substituted azulenes by the Hafner method [10, 11]. Hetaryl-substituted pyrylium perchlorates have not been previously used in this reaction. The Hafner method was subsequently modified by the use of cyclopentadienyllithium in dry ether instead of cyclopentadienylsodium in tetrahydrofuran (THF); this made it possible to synthesize azulenes IV-VI in higher yields.

Whereas azulenes IV and V were obtained in 62 and 64% yields, respectively, and azulene VI was obtained in 5-10% yield by the Hafner method [10, 11], these azulenes were obtained in 82, 83, and 60% yields, respectively, by our modified method.

The compositions and structures of the synthesized azulenes were proved by elementary analysis and data from IR and UV spectroscopy. The introduction of a thienyl residue in place of a methyl group in the 6 position of 2,6,8-trimethylazulene gives rise to a 15-nm bathochromic shift of the principal maximum as compared with the shift of 2,4,6-trimethylazulene. (Scheme, top, following page.)

To ascertain the effect of an azulene substituent on the properties of the pyrylium cation and to synthesize inaccessible azulenes with substituents in the five- and seven-membered rings, we subjected azulenes IV and VI to reaction with 2,6-diphenylpyrylium perchlorate. Reactions of this sort have been previously described only for 2,6-diphenyl-4-chloro-substituted pyrylium perchlorate and 4,6,8-trimethylazulene [12]. We were able to introduce azulene directly in the 4 position of the γ-unsubstituted pyrylium cation.

Absorption bands of the pyrylium cation and the ClO_4^- anion appear in the IR spectra of the pyrylated azulenes [13]. It was found that the presence of an azulene substituent does not have a substantial effect on the properties of the pyrylium cation, and this made it possible to synthesize α,α-diphenyl-γ-[4,8-dimethyl-6-(2-thienyl)-1-azulenyl]pyridine by treatment of α,α-diphenyl-γ-[4,8-dimethyl-6-(2-thienyl)-1-azulenyl]pyrylium perchlorate with ammonia or ammonium acetate.

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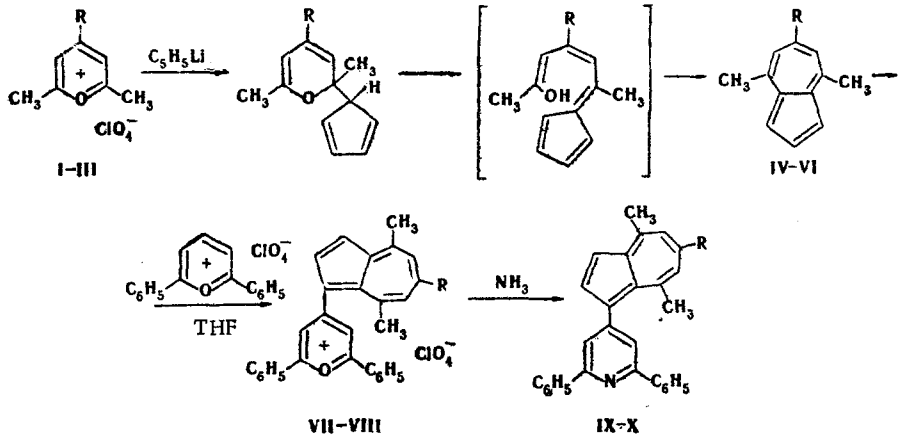

I, IV, VII, IX R=CH_3, II, V, VIII, X R=α-thienyl III, VI R= benzothiazolyl

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with UR-20 spectrometer (with an NaCl prism). The UV spectra of solutions of the compounds in ethanol (10^{-4}-10^{-5} M) were recorded with a Specord UV-vis spectrophotometer. The characteristics of the synthesized compounds are presented in Table 1.

4,8-Dimethyl-6-(2-thienyl)azulene (V). A 1.3-g (20 mmole) sample of freshly distilled cyclopentadiene was metallated with butyllithium in 40 ml of ether in a nitrogen atmosphere for 2 h, after which 1.45 g (5 mmole) of 2,6-dimethyl-4-(2-thienyl)pyrylium perchlorate in 5 ml of THF was added, and the reaction mixture was heated at 35°C for 6 h. It was then cooled and poured into 100 ml of water, and the ether layer was separated, dried over sodium sulfate, and evaporated. The 4,8-dimethyl-6-(2-thienyl)azulene was extracted with petroleum ether.

4,8-Dimethyl-6-(2-benzothiazolyl)azulene (VI). Cyclopentadienyllithium, obtained from 1.3 g (20 mmole) of cyclopentadiene and butyllithium, was subjected to reaction with 1.7 g (5 mmole) of 2,6-dimethyl-4-(2-benzothiazolyl)pyrylium perchlorate. The reaction was carried out at room temperature for 1 h, and the resulting mixture was refluxed for 4 h. The desired product was isolated as in the preceding case.

4,6,8-Trimethylazulene (IV). This compound, with mp 81°C (mp 81-82°C [10]), was obtained from cyclopentadienyllithium and 1.1 g (5 mmole) of 2,4,6-trimethylpyrylium perchlorate.

α,α-Diphenyl-γ-(4,6,8-trimethyl-1-azulenyl)pyrylium Perchlorate (VII). A solution of 1 g (3.3 mmole) of 2,6-diphenylpyrylium perchlorate and 0.256 g (1.5 mmole) of 4,6,8-trimethylazulene in 10 ml of dry dimethylformaldehyde (DMF) was refluxed for 2 h, after which it was cooled and treated with ether, and the precipitated crystals of the desired product were removed by filtration.

α,α-Diphenyl-γ-[4,8-dimethyl-6-(2-thienyl)-1-azulenyl]pyrylium Perchlorate (VIII). This compound was obtained as in the preceding experiment from 1 g (3 mmole) of 2,6-diphenylpyrylium perchlorate and 0.36 g (1.5 mmole) of 4,8-dimethyl-6-(2-thienyl)azulene.

α,α-Diphenyl-γ-[4,8-dimethyl-6-(2-thienyl)-1-azulenyl]pyridine (X). A mixture of 0.57 g (1 mmole) of α,α-diphenyl-γ-[4,8-dimethyl-6-(2-thienyl)-1-azulenyl]pyrylium perchlorate and 0.77 g (1 mmole) of ammonium acetate in alcohol was refluxed for 1 h, after which the solvent was removed by distillation, and the residue was treated with ether. The ether extract was evaporated, and the residue was recrystallized from alcohol.

α,α-Diphenyl-γ-(4,6,8-trimethyl-1-azulenyl)pyridine (IX). This compound was synthesized from 0.25 g (0.5 mmole) of α,α-diphenyl-γ-(4,6,8-trimethyl-1-azulenyl)pyrylium perchlorate and 0.77 g (1 mmole) of ammonium acetate. The reaction product was purified by chromatography with a column filled with aluminum oxide (elution with chloroform).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	IR spectra, cm^{-1}	UV spectra (in alcohol), λ_{max}, nm (log ε)	Found, %					Empirical formula	Calc., %					Yield, %
				C	H	Cl	N	S		C	H	Cl	N	S	
IV	81	1580, 1330, 1220, 1080	205 (4,26), 248 (4,35), 290 (4,5), 339 (3,52), 355 (3,61), 565 (2,3)	—	—	—	—	—		—	—	—	—	—	82
V	100—102	1580, 1550, 1425, 1220, 860, 770	205 (4,48), 245 (4,36), 264 (4,2), 292 (4,08), 327 (4,60), 580 (2,8)	80,3	5,8	—	—	13,3	$C_{16}H_{14}S$	80,6	5,9	—	—	13,4	83
VI	117—118	1580, 1540, 1315, 1230, 1080, 940, 810, 770, 720	—	78,4	5,0	—	4,6	10,9	$C_{19}H_{15}NS$	78,8	5,2	—	4,8	11,0	60
VII*	276 (dec)	1620, 1580, 1540, 1320, 1220, 1100	—	71,6	4,9	6,8	—	—	$C_{30}H_{25}ClO_5$	71,9	5,0	7,0	—	—	48
VIII	260 (dec)	1625, 1600, 1580, 1540, 1100, 960, 870, 730	—	69,2	4,3	6,6	—	5,6	$C_{33}H_{25}SClO_5$	69,6	4,9	6,2	—	5,6	52
IX	97—98	1610, 1600, 1580, 1540, 1260, 1080	—	89,9	6,0	—	3,2	—	$C_{30}H_{25}N$	90,2	6,3	—	3,5	—	67
X	133—134	1610, 1600, 1580, 1540, 1080, 960, 870, 730	—	84,6	5,1	—	2,6	6,3	$C_{33}H_{25}NS$	84,7	5,3	—	2,9	6,8	65

*According to the data in [12], this compound has mp 255°C.

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SYNTHESIS OF SOME THIENYL-SUBSTITUTED α,β-UNSATURATED KETONES CONTAINING A NITRO GROUP

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A method for the condensation of nitroformylthiophenes with ketones of the aromatic and heterocyclic series by means of ammonium acetate in glacial acetic acid was developed. The method makes it possible to obtain thienyl-substituted α,β-unsaturated ketones with a nitro group in the heterocyclic ring.

Crotonic condensation is the most convenient and widely used method for the synthesis of α,β-unsaturated aromatic and heterocyclic ketones. Depending on the character of the reacting substances, either acids (usually H_2SO_4, HCl, or $AlCl_3$) [1, 2] or compounds with basic character (NaOH, KOH, amines, carbonates and bicarbonates of metals, or other compounds [3-5]) can be used as catalysts for this reaction. However, in a number of cases when nitro groups are present in the starting aldehydes and ketones, the known methods for crotonic condensation do not make it possible to obtain unsaturated carbonyl compounds. Thus, for example, the condensation of 5-nitro-2-formylthiophene with acetone cannot be realized in either alkaline or acidic media [1]. Unsaturated carbon l compounds that contain a system of conjugated C=C and C=O bonds display biological activity [6]. However, the introduction of a nitro group in the heterocyclic ring of unsaturated ketones markedly intensifies their specific biological action.

However, the direct introduction of a nitro group in unsaturated ketones is usually hindered both by the presence in the molecule of several reaction centers that decrease the selectivity of nitration significantly and by the relative instability of the double bond, which displays a capacity for hydrolysis and oxidation in acidic or alkaline media.

For the synthesis of thienyl-substituted α,β-unsaturated ketones that contain a nitro group in one of the positions of the heterocyclic ringwe therefore used crotonic condensation in glacial acetic acid. As the catalyst of this reaction we used for the first time ammonium

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