REACTION OF 2-ARYLIDENE-5-METHYLCYCLOPENTANE-1,3,4-TRIONE WITH β-AMINOVINYLCARBONYL COMPOUNDS

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A simple method is proposed for the synthesis of the previously unknown 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-triones, 2,5-dimethyl-6-R-7-phenyl-4,7-dihydro-4-azaindane-1,3-diones, and their derivatives from 2-arylidene-5-methylcyclopentane-1,3,4-trione and β-aminovinylcarbonyl compounds.

It has already been shown that polynuclear nitrogen-containing compounds, 4-azafluorene derivatives [1], and benzoyleneketoquinolines [2] are formed by the reaction of 2-arylideneindane-1,3-diones with β-aminovinylcarbonyl compounds. In this paper we describe a similar reaction between 2-arylidene-5-methylcyclopentane-1,3,4-triones (Ia, b) and β-aminovinylcarbonyl compounds [3, 4]. As a result of this comparatively simple reaction, we were able to synthesize complex heterocyclic systems containing dihydropyridine and β- (or α-) diketone groupings (IVa-i, VIa,b, and V). The β-aminovinylcarbonyl compounds that we used were 3-amino- and 3-alkylamino-5,5-dimethyl-2-cyclohexen-1-ones (IIa-e), ethyl β-aminocrotonate (IIIa), and bisacetonitrile (IIIb).

Except for the condensation of Ia with IIIa, which proceeded only on fusing the components, the reactions were carried out in ethanol. Compounds IVa-i and VIa,b are yellow or orange crystalline substances which are quite soluble in polar solvents. N-Substituted compounds IVb-f,h,i form dark-blue solutions with sodium alcoholates, while N-unsubstituted IVa,g and VIa,b form bright-red solutions with sodium alcoholates. The reaction products were separated and purified by means of column chromatography with Al_2O_3.

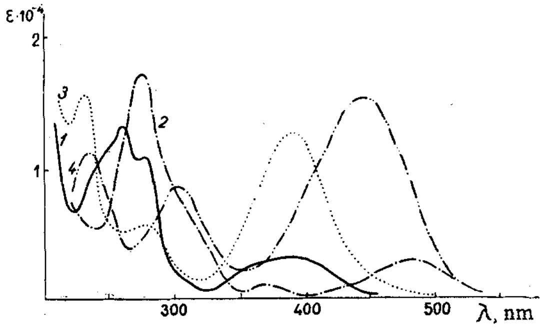

Fig. 1. UV absorption spectra of 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (IVa) and 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,2,8-trione: 1) IVa in ethanol; 2) IVa in alkaline ethanol solution; 3) V in ethanol; 4) V in alkaline ethanol solution.

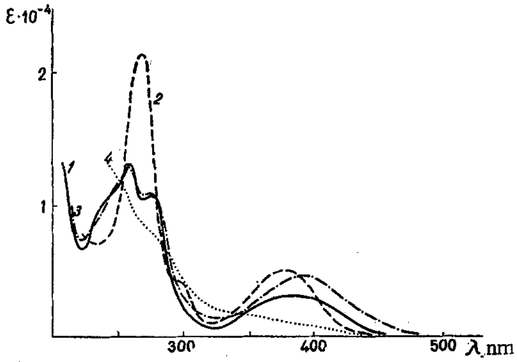

Fig. 2. UV absorption spectra of IVa and its derivatives in ethanol: 1) IVa; 2) VII; 3) VIII; 4) IX.

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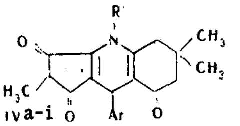
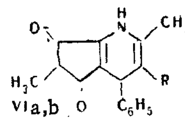
TABLE 1.


IVa-i


VIa,b

Comp.	Ar	R′(R)	mp*	Empirical formula	Found, %			Calculated, %			Yield, %	IR spectrum, cm^{-1}†
					C	H	N	C	H	N		
IV a	C_6H_5	H	140	$C_{21}H_{21}NO_3$	74,7	6,5	4,2	75,2	6,3	4,2	23	1500 s 1598 m 1624 w 1656 m 1696 s 1742 m
IV b	C_6H_5	CH_3	154—156	$C_{22}H_{23}NO_3$	75,7	7,1	4,1	75,6	6,6	4,0	50	1560 s 1629 sh 1640 s 1683 s 1737 m
IV c	C_6H_5	C_4H_9	130	$C_{25}H_{29}NO_3$	76,3	7,4	3,4	76,7	7,5	3,6	46,5	1561 m, 1628 s 1650 s 1681 s 1740 s
IV e	C_6H_5	CH_2COOCH_3	190	$C_{24}H_{25}NO_5$	70,7	6,5	3,6	70,8	6,2	3,4	11,5 ‡	1562 s 1639 s 1688 s 1738 m 1752 s
IV f	C_6H_5	$CH_2COOC_2H_5$	190—192	$C_{25}H_{27}NO_5$	71,0	6,6	3,1	71,0	6,7	3,3	24,5 ‡	1563 s 1640 s 1686 s 1744 s
IV g	3,4,5-$(CH_3O)_3C_6H_2$	H	180—181	$C_{24}H_{27}NO_6$	67,4	6,6	3,6	67,8	6,4	3,3	14,4	1499 s 1594 s 1633 m 1650 m 1694 s 1741 m
IV h	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	184—186	$C_{25}H_{29}NO_6$	68,5	7,1	3,5	68,3	6,7	3,2	42	1563 m 1588 m, 1643 s 1684 s 1740 m
IV i	3,4,5-$(CH_3O)_3C_6H_2$	$CH_2COOC_2H_5$	138—140	$C_{28}H_{33}NO_8$	65,4	6,7	3,3	65,7	6,5	2,8	20 ‡	1570 s 1590 m 1640 s 1690 s 1739 s 1754 s
V	—	—	250	$C_{21}H_{21}NO_3$	75,0	6,5	4,3	75,2	6,3	4,2	13	1584 m 1642 s 1669 m 1755 m
VI a	—	$COOC_2H_5$	198—200	$C_{19}H_{19}NO_4$	70,3	5,9	4,4	70,1	5,9	4,3	16	1603 m 1642 s 1658 s 1686 s 1741 m
VI b	—	CN	195	$C_{17}H_{14}N_2O_2$	73,6	5,4	10,2	73,4	5,1	10,0	13,5	1605 m 1658 s 1689 s 1740 m 222 s

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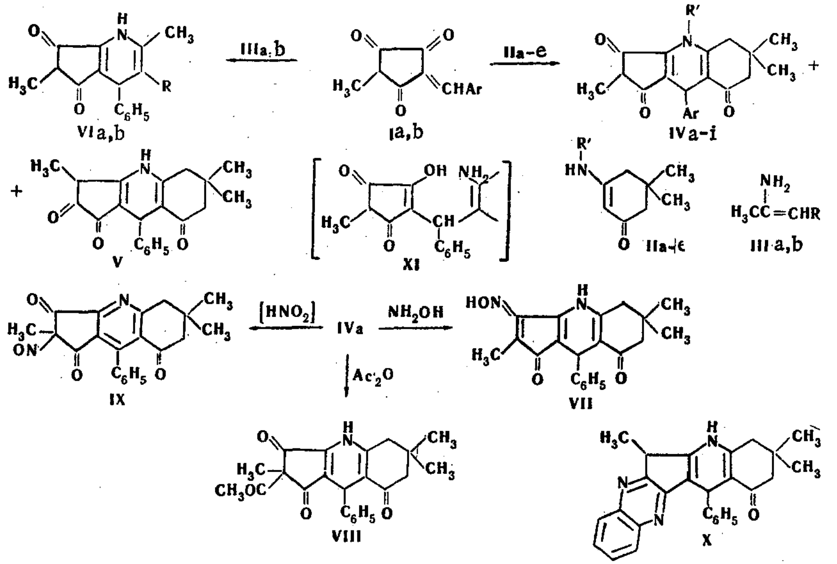
*Aqueous acetone was used to crystallize IVc,f,h,i; methanol was used for IVb; and aqueous ethanol was used for IVg.

† ν_{NH}: IVa 3165 m, 3230 m, 3292 sh, 3350 sh; IVg 3172 m, 3221 w; V 3116 m, 3186 s, 3239 m; VIa 3159 sh, 3310 s; VIb 3110 w, 3220 sh, 3260 s.

‡ The yields for IVe from IId in methanol, for IVi from IId in ethanol, and for IVf from IIf are indicated.

Two compounds with mp 140° (IVa) and 250° (V) and the same elementary composition but different UV spectra (Fig. 1), IR absorption spectra (Table 1), and reactivities were obtained by the condensation of Ia with IIa. From the mechanism proposed for reaction through XI, one might have expected the formation of two isomers, viz., 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (IVa) and 2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,2,8-trione (V). The α-diketone grouping of V was proved by obtaining the corresponding quinoxaline (X) with o-phenylenediamine. The reactivity of IVa was investigated. Compound IVa reacts with hydroxylamine to give oxime VII without oxidation of the dihydropyridine ring, as is usual in the oximation of similar 3,5-diacyl-1,4-dihydropyridine systems [5]. The IR spectrum of VII does not contain a ν_{CO} band at 1742 cm^{-1}, and a $\nu_{C=N}$ band appears at 1672 cm^{-1}. Compound IVa reacts with acetic anhydride in the presence of sodium acetate to give a 2-acetyl derivative (VIII), the IR spectrum of which contains, in addition to bands characteristic for IVa, a ν_{CO} band at 1723 cm^{-1}, which corresponds to a new keto group, while ν_{NH} does not change. The UV spectra of VII and VIII are similar to the spectrum of IVa (Fig. 2). Nitroso derivative IX is obtained by treatment of IVa with nitrous acid. In this case, the dihydropyridine ring is oxidized to a pyridine ring.

The ν_{NH} band is absent in the IR spectrum of IX, and ν_{CO} increases to the value characteristic for 2,2-disubstituted 4-azaindane-1,3-diones [6] (Table 1). The UV spectrum of IX differs markedly from the UV spectra of IVa, VII, and VIII (Fig. 2).



Ar = C_6H_5, 3,4,5-$(CH_3O)_3C_6H_2$; R = $CO_2C_2H_5$, CN; R′ = H, CH_3, C_4H_9, CH_2CO_2H, $CH_2CO_2C_2H_5$, $CH_2CO_2CH_3$

We then synthesized a whole series of hydrobenzazaindanetriones (IVb-i) and dihydroazaindanediones (VIa,b) starting from Ia,b, IIb-e, and IIIa,b. It is interesting to note that IVd (R′ = CH_2COOH) could not be obtained in pure form, since esterification of the carboxyl group to form esters (IVe,f,i) occurs during the condensation of Ia,b with IId (R′ = CH_2COOH) in methanol or ethanol. The structure of IVf was proved by alternative synthesis from Ia and IIe (R′ = $CH_2COOC_2H_5$), and IVe was formed by the action of diazomethane on unpurified IVd, which was separated from IVe by means of aqueous sodium bicarbonate. Compound Ia could not be condensed with IId (R′ = CH_2COOH) in acetic acid.

The UV absorption spectra of IVa-i and VIa,b in neutral media (ethanol) are similar, which indicates their structural similarity. The similarity of these compounds is also observed in the IR spectra (Table 1). There are a number of intense bands at 6 μm, and the bands of vibrations above 1700 cm^{-1} belong to the ester group in IVe,f,i or to a keto group which is not in conjugation with the nitrogen atom. In some cases these vibrations overlap and give one very intense absorption band (IVe,f). The remaining bands correspond to ν_{CO} and $\nu_{C=C}$ of a conjugated system. All of the N-unsubstituted compounds (IVa,g, V, and VIa,b) have a ν_{NH} band in the 3-μm region (Table 1). An intense $\nu_{C\equiv N}$ band appears at 2224 cm^{-1} in the spectrum of VIb.

EXPERIMENTAL

2,6,6-Trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (IVa). A mixture of solutions of 0.5 g (2.34 mmole) of Ia in 15 ml of ethanol and 0.326 g (2.34 mmole) of IIa in 5 ml of ethanol was refluxed for 20 min. The ethanol was removed, and the bright-yellow residue was dissolved in a small amount of acetone and chromatographed with a column filled with Al_2O_3 (2.4 × 75 cm). The first colored zone was eluted with ethyl acetate and evaporated to dryness to give 0.18 g of IVa as a yellow crystalline substance with mp 140° (from aqueous acetone). The product was soluble in polar solvents. It formed a bright-red solution with sodium alcoholate. Found: mol. wt. 335 (mass spectrum). Calculated: mol. wt. 335.4.

2,6,6-Trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,2,8-trione (V). A second fraction was eluted with ethanol from the column after removal of IVa and was evaporated to dryness to give 0.1 g (13%) of yellow crystals of IVb which decomposed at 250° (from aqueous acetone) and formed an orange-yellow solution with sodium ethoxide. A third band was eluted from the column with water. Filtration and evaporation of this fraction yielded a yellow crystalline product which did not contain nitrogen. The structure of this compound was not established.

3-Oximino-2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,8-dione (VII). A mixture of 1.0 g (10 mmole) of hydroxylamine hydrochloride, 5 ml of water, and 10 ml of 0.1 N NaOH was added to a solution of 0.5 g (1.5 mmole) of IVa in 15 ml of ethanol, and the mixture was refluxed for 45 min. The solution was poured into water to precipitate 0.35 g (67%) of greenish-yellow VII with mp 245° (decomp., from ethanol). Found %: C 72.3; H 6.5; N 8.1. $C_{21}H_{22}N_2O_3$. Calculated %: C 72.0; H 6.3; N 8.0.

2-Nitroso-2,6,6-trimethyl-9-phenyl-5,6,7,8-tetrahydrobenz[*f*]-4-azaindane-1,3,8-trione (IX). Sodium nitrite (about 0.5 g) was added in small portions with cooling and stirring to a solution of 0.2 g (0.6 mmole) of IVa in 10 ml of acetic acid and 2 ml of hydrochloric acid (1 : 1) until the solution stopped, giving a red solution with sodium methoxide. The mixture was allowed to stand for 24 h at room temperature and diluted with water to isolate 0.15 g (68%) of a yellow precipitate of IX with mp 140° (from acetic acid – water). Found %: N 7.7. $C_{21}H_{18}N_2O_4$. Calculated %: N 7.7.

1-Oxo-3,3,6-trimethyl-13-phenyl-1,2,3,4,5,13-hexahydro-6H-5-azabenz[5,6]indeno[2,3-b]quinoxaline (X). A mixture of 1 g (2.98 mmole) of V, 0.33 g (3.06 mmole) of o-phenylenediamine, 10 ml of 3% NaOMe, and 100 ml of absolute ethanol was refluxed for 15 min. The mixture was then chromatographed through a column filled with Al_2O_3 by elution with ethyl acetate and then ethanol to give 0.1 g (8.3) of X with mp 185° (decomp., from aqueous ethanol). Found %: N 10.8. $C_{27}H_{25}N_3O$. Calculated %: N 10.3.

2-Acetyl-2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (VIII). Sodium acetate [0.2 g (2.44 mmole)] was added to a solution of 0.4 g (0.12 mmole) of IVa in 20 ml of acetic anhydride, and the mixture was refluxed for 4 h and poured into water to precipitate 0.2 g (49%) of yellow crystals of VIII with mp 246° (from ethanol). The product gave a red coloration with sodium methoxide. Found %: C 73.5; H 6.3; N 3.7. $C_{23}H_{23}NO_4$. Calculated %: C 73.2; H 6.1; N 3.7.

2,5-Dimethyl-6-carbethoxy-7-phenyl-4,7-dihydro-4-azaindane-1,3-dione (VIa). A total of 2 g (9.35 mmole) of Ia and 1.22 g (9.45 mmole) of IIIa was fused at 80-90° for 5 min, dissolved in 20 ml of acetone, applied to a column filled with Al_2O_3, and eluted with ethyl acetate. The first colored fraction was collected and evaporated to dryness to give 0.5 g of bright yellow VIa.

4-Carbethoxymethyl-2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (IVf). A mixture of 2 g (9.35 mmole) of Ia and 1.84 g (9.35 mmole) of IId was refluxed in 50 ml of absolute ethanol for 7 h. All of the ethanol was removed, and the bright-yellow residue was dissolved in saturated $NaHCO_3$. The insoluble part was filtered and washed with $NaHCO_3$ solution and water to give 0.8 g (20%) of yellow crystals of IVf.

4-Carbomethoxymethyl-2,6,6-trimethyl-9-phenyl-4,5,6,7,8,9-hexahydrobenz[*f*]-4-azaindane-1,3,8-trione (IVe). A mixture of 1 g (4.68 mmole) of Ia and 0.92 g (4.68 mmole) of IId was refluxed in 40 ml of absolute methanol for 7 h. All of the methanol was removed, and the bright-yellow residue was dissolved in saturated $NaHCO_3$ solution. The insoluble part (IVe) was separated and washed with $NaHCO_3$ solution and water to give 0.2 g (11.5%) of yellow crystals of IVe. The filtrate was acidified with dilute HCl, filtered, and dried. The yellow substance obtained (0.5 g) was dissolved in 20 ml of dioxane, and an ether solution of diazomethane, prepared from 0.5 g (4.85 mmole) of nitrosomethylurea and 1.5 ml of 50% KOH in 5 ml of ether, was added to it. The reaction mixture was allowed to stand for 24 h at room temperature, evaporated to dryness, applied to a column (2.4 × 75 cm), and eluted with ethyl acetate. The first colored fraction was collected and evaporated to give 0.3 g of yellow crystals of IVe. The overall yield was 0.5 g (28.8%).

2-(3,4,5-Trimethoxybenzylidene)-5-methylcyclopentane-1,3,4-trione (Ib). A total of 1.9 g (8.4 mmole) of the glyoxylic ester of 5-methylcyclopentane-1,3,4-trione and 1.65 g (8.4 mmole) of 3,4,5-trimethoxybenzaldehyde were dissolved in 10 ml of ethanol, a solution of 1.18 g of NaOH in 50 ml of distilled water was added, and the mixture was shaken at room temperature for 24 h. Dilute HCl precipitated 1.8 g (70%) of bright-yellow crystals of Ib with mp 210° (from ethanol). Found %: C 63.6; H 5.5. $C_{16}H_{16}O_6$. Calculated %: C 63.2; H 5.3.

The UV spectra of 10^{-4} M ethanol solutions with a layer thickness of 1 cm were obtained with an SF-4 spectrophotometer. The IR spectra of mineral oil suspensions (VIa,b, Vc, VIII, and IX in hexachlorobutadiene) were obtained with an IKS-14 spectrophotometer from 1400-1800 cm^{-1} with a NaCl prism and from 3000 to 3500 cm^{-1} with a LiF prism. The mass spectrum was obtained with an MKh-1303 mass spectrometer.

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