A STUDY OF 1,2,3,4-TETRAHYDRO-4-AZAFLUORENE-3,9-DIONES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 305–311, 1969

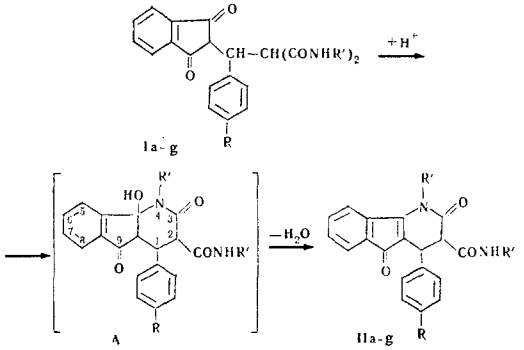
UDC 547.665'678.3:822.3:543.422.4.6

Intramolecular cyclization of the diamides and N,N'-dimethylamides of α-[indan-1,3-dion-2-yl]benzylmalonic acids (I) has given 1-aryl-2-carbamoyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-diones and 1-aryl-4-methyl-2-methylcarbamoyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-diones (II). The structure of compounds II was shown by chemical methods: bromination, xanthylation, and hydrolysis in alkaline and acid media, and also by a study of IR and UV spectra.

Continuing investigations [1–3] on the synthesis and reactivity of amide derivatives of cyclic β-diketones, we set ourselves the aim of studying the intramolecular reaction of the amide group NH with the carbonyl group of derivatives of indan-1,3-dione. For this purpose we selected the diamides of α-[indan-1,3-dion-2-yl] benzylmalonic acids (**Ia–g**), which are formed by the addition of malondiamides to 2-arylideneindan-1,3-diones [3].

In an acid medium, the intramolecular condensation of the carbonyl group of the indandione and an NH group of the malondiamide residue of compounds **Ia–g** takes place. This gives rise to derivatives of a new nitrogen-containing heterocycle, 1,2,3,4-tetrahydro-4-azafluorene-3,9-diones (**IIa–g**).

We first showed the possibility of this condensation with compounds **Ia–d** [4].



a R = R' = H; b R = NO_2, R' = H; c R = Cl, R' = H; d R = OCH_3, R' = H; e R = H, R' = CH_3; f R = NO_2, R' = CH_3; g R = Cl, R' = CH_3

Condensation is favored by the spatially suitable arrangement of the two groups and also by the possibility of the formation of an unstrained six-membered ring. However, the decisive role in the condensation is played by the pH of the medium. In a neutral medium no condensation takes place when **Ia** is subjected to prolonged heating in ethanol. Instead of this, a retro-Michael cleavage of **Ia** into benzylideneindan-1,3-dione and malondiamide takes place. It is known that condensations of NH groups with carbonyl groups are catalyzed by acids [2,5–9], and with a decrease in the nucleophilicity of the attacking agent, a decrease in the pH of the medium is necessary [9]. The condensation of compounds I to form compounds II takes place normally only in an acid medium, the rate of the reaction depending on the strength of the acid. In acetic acid, cyclization requires heating for several hours. The addition of p-toluenesulfonic acid accelerates the reaction considerably. In concentrated hydrochloric acid, condensation takes place even at room temperature.

Compounds **IIa–g** are also formed by the prolonged heating of the 2-arylideneindan-1,3-diones with malondiamide and N,N'-dimethylmalondiamide in acetic acid. Evidently, the addition of the malondiamide to the double bond of the 2-arylideneindan-1,3-diones takes place first, with the subsequent cyclization of the I formed into II. A similar simultaneous addition and cyclization has been shown in the reaction of 2-arylidene-1,3-diones with aminovinylcarbonyl compounds [10].

The mechanism of this intramolecular condensation of compound I is a nucleophilic addition of the amide NH group to the carbonyl group, with the subsequent splitting out of water and the formation of II.

The nucleophilicity of the nitrogen atom plays an important part in the condensation. Alkyl substituents on the nitrogen, having a positive inductive effect, increase the electron density on the nitrogen and favor the condensation. Conversely, the introduction of a phenyl radical (I, R = H, Cl, NO_2; R' = C_6H_5) decreases the electron density on the nitrogen to such an extent that condensation does not take place under the conditions given.

The derivatives of tetrahydro-4-azafluorene-3,9-diones (II) obtained, in contrast to the colorless initial diamides (I), are red-orange crystalline substances with high melting points (Table 1). The lowering of the melting point for the N-methyl derivatives **IIe-g** as compared with those for compounds **IIa–d**, unsubstituted on the nitrogen atom, shows the strong intramolecular association of the latter. Compounds II dissolve in concentrated sulfuric acid with an intense blue coloration, which is not given by 1-aminoind-2-en-3-ones [11]. This color reaction is a new qualitative reaction for compounds containing the tetrahydro-4-azafluorenedione system. The coloration is evidently connected with the protonation of the molecule and the formation of a conjugated cation. When the sulfuric acid solutions are diluted, compounds II are recovered unchanged. Compounds **IIa–d** possess some acidic properties. They dissolve in aqueous and alcoholic alkalis with the formation of violet-red solutions.

In acetic acid solution, compounds II undergo bromination. Even when an excess of bromine is used, only the monobromo derivative III is formed; its structure being confirmed by IR spectra.

Table 1

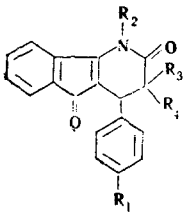
Characteristics of the Compounds Synthesized

Compound	Mp, °C	Empirical formula	Found, %				Calculated, %				Number of labile hydrogen atoms*	Yield, %
			C	H	N	halogen	C	H	N	halogen		
IIf	201—203	$C_{21}H_{17}N_3O_5$	64.56	4.28	10.50	—	64.44	4.38	10.73	—	not investigated	73
IIg	146—148	$C_{21}H_{17}ClN_2O_3$	65.95	4.66	7.48	9.24	66.23	4.49	7.35	9.31	„ „	75
III	220—222	$C_{19}H_{13}BrN_2O_3$	57.28	3.33	6.97	19.73	57.45	3.29	7.05	20.12	„ „	74
IV	304—306	$C_{32}H_{22}N_2O_4$	77.41	4.25	5.92	—	77.10	4.45	5.62	—	„ „	51—56
V	182—183	$C_{19}H_{16}N_2O_4$	—	—	8.13	—	—	—	8.36	—	1	47
VIa	173—174	$C_{19}H_{15}NO_5$	62.08	4.68	4.20	—	67.75	4.45	4.15	—	2	70
VIb	156—158	$C_{19}H_{14}N_2O_7$	59.93	3.54	7.55	—	59.68	3.69	7.32	—	2	65
VIc	146—148	$C_{19}H_{14}ClNO_5$	61.28	3.62	3.56	9.61	61.38	3.79	3.76	9.53	2	59
VIIa	239—240	$C_{18}H_{13}NO_2$	78.35	4.64	5.07	—	78.53	4.76	5.08	—	not investigated	45
VIIb	262—264	$C_{18}H_{12}N_2O_4$	67.33	3.91	8.90	—	67.49	3.77	8.74	—	„ „	52
VIII	101—105	$C_{18}H_{15}NO_3$	—	—	4,60	—	—	—	4.77	—	1	59
IX	171—173	$C_{19}H_{14}O_6$	74.28	4.71	—	—	74.50	4.60	—	—	1+1 (enolic)	45
X	110—111	$C_{23}H_{22}O_6$	69.83	5.41	—	—	70.06	5.62	—	—	not investigated	56

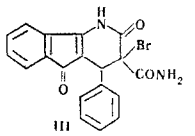
*From the results of potentiometric titration.

Table 2

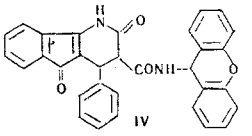
Infrared Spectra of the Substituted 1, 2, 3, 4-Tetrahydro-4-azafluorene-3, 9-diones



Compound	R_1	R_2	R_3	R_4	ν_{CO}	$\nu_{C=O}$	ν_{arom}	ν_{NO_2}	ν_{NH}
IIa	H	H	H	$CONH_2$	1702(61), 1673(79), 1659(45) Shoulder	1621(65)	1587(63)	—	3417(63), 3340(55), 3305(68), 3255(65), 3175(73)
IIb	NO_2	H	H	$CONH_2$	1712(70), 1686(80)	1637(60)	1592(50)	1520(70)	3480(62), 3359(62), 3212(35), 3112(60)
IId	OCH_3	H	H	$CONH_2$	1708(50), 1673(73), 1658(45) Shoulder	1628(58)	1589(50)	—	3399(70), 3307(42), 3266(60), 3208(78), 3116(60)
IIe	H	CH_3	H	$CONHCH_3$	1703(45) 1688(65), 1666(62)	1618(45)	1587(50)	—	3384(40), 3356(35), 3258(80), 3089(69)
IIg	Cl	CH_3	H	$CONHCH_3$	1701(60), 1688(72), 1668(50)	1623(55)	1584(50)	—	3377(60), 3241(55)
III	H	H	Br	$CONH_2$	1724(70), 1677(80), 1656(50)	1620(45)	1584(60)	—	3445(50), 3339(30), 3266(45), 3212(50)
IV	H	H	H	CONHXanth	1720(20), 1656(70)	1634(60)	1606(25)	—	3301(30)
VII	H	H	H	H	1701(70), 1671(75)	1622(65)	1582(70)	—	3232(72), 3188(78)



III

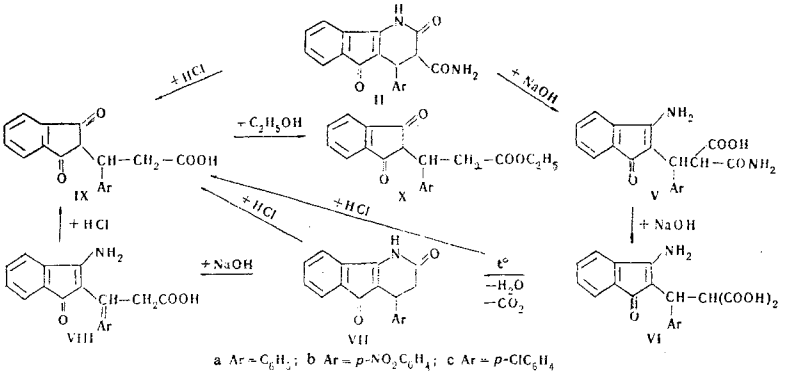


IV

Xanthydrol reacts with the exocyclic amide groups of compounds II forming the monoxanthenyl derivatives

sorption of the NH groups of the lactams (VII, IIa-d) and of the secondary amides (IIa-g).

In the IR spectra, strong absorption at about 250 nm which shifts bathochromically to 265 nm in an alkaline medium is characteristic for compounds II. The color of the substances is due to the comparatively low maximum in the 430–480 nm region.



a Ar = C_6H_5; b Ar = p-$NO_2C_6H_4$; c Ar = p-ClC_6H_4

IV. Identical compounds are formed by the more prolonged heating of the noncyclic diamides I with xanthydrol in acetic acid solution. Obviously, during the reaction both the cyclization of I to II and xanthenylation take place.

The structure of the compounds synthesized was confirmed by their IR and UV spectra. The IR spectra of compounds II (Table 2) differ strongly in the 6 μ region from the 4-azafluoren-9-ones [12] and the 1,4-dihydro-4-azafluoren-9-ones [13]. In the latter, particularly those containing a bis(ketovinyl)amine group, the absorption frequency of the individual groups is low and they are difficult to identify. In the derivatives of 1,2,3,4-tetrahydro-4-azafluorene-3,9-diones, the chain of conjugation is shorter and they are closer in structure to the cyclic acylaminoindenones [14]. In the 6 μ region, compounds II absorb in the 1702–1701 cm^{-1} region, which corresponds to the stretching vibrations of the carbonyl group of indenone [15]. The absorption in the 1688–1771 cm^{-1} region relates to the frequencies of the carbonyl group of a cyclic six-membered lactam [16]. Amide carbonyl groups absorb at lower frequencies, in the 1668–1656 cm^{-1} region [17]. What has been said is confirmed by the spectrum of VII, in which absorption is lacking in the region of amide carbonyls, while the bands of the lactam carbonyl remain unchanged. In some cases, the frequencies of the absorption of the carbonyl groups of the lactam and amide groups overlap. In compounds II the frequency of the double bond of the five-membered ring of the indenone and those of the aromatic rings also appear in the 6 μ region. Compound IIb also has the characteristic absorption of the nitro group. The free and associated vibrations of an NH group appear in the 3 μ region. We ascribe the highest frequencies at about 3400 cm^{-1} to the NH frequencies of the unsubstituted exocyclic amide group of compounds IIa–d and III. The remaining frequencies are due to the ab-

In contrast to the 4-azafluoren-9-ones [18], the 1,2,3,4-tetrahydro-4-azafluorene-3,9-diones are readily hydrolyzed by alkalis. The hydrolysis of compounds II in 1N caustic soda solution takes place with the cleavage of the lactam ring and the formation of the monoamide of α-[1-aminoind-2-en-3-on-2-yl]benzylmalonic acid (V). The resulting monoamide V hydrolyzes further in an alkaline medium to α-[1-aminoind-2-en-3-on-2-yl]benzylmalonic acid (VI), which is the final product of the alkaline hydrolysis of II. The acid VI is also formed directly from II on more prolonged heating in alkali. The hydrolysis of the lactam ring of II at the 3—4 bond is confirmed by IR spectra, in which, in addition to the carbonyl frequencies of the acid, the characteristic absorption of the aminoindenones [14] appears. The dibasicity of the acid VI was established by potentiometric titration.

The hydrolysis of compounds II in an acid medium takes place more slowly and leads to the formation of nitrogen-free compounds. The final product of the acid hydrolysis of II is β-(indan-1,3-dion-2-yl)propionic acid (IX). The acid IX is also formed from V and VI under the conditions of acid hydrolysis. The presence of two labile hydrogen atoms (enolic and carboxylic) in the molecule of IX was established by potentiometric titration.

On being heated in inert solvents, the dicarboxylic acid VI decarboxylates. Intramolecular acylation of the free amino group by the carboxyl group and ring closure take place simultaneously. The 1-phenyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (VII) formed resembles compounds II in structure and properties but differs from them by the absence of an amide group in position II. Closure of the lactam ring is confirmed by the IR spectra and the formation of a blue coloration when VII is dissolved in concentrated sulfuric acid, which is characteristic for derivatives of 1,2,3,4-tetrahydro-4-azafluorene-3,9-dione. Compound VII

contains a lactam ring and is readily hydrolyzed by alkalis. In acids, the β-[1-aminoinden-2-en-3-on-2-yl]-β-phenylpropionic acid (VIII) obtained by alkaline hydrolysis, hydrolyzes further to IX. For the complete identification of the acid IX, its ethyl ester X was prepared.

The characteristics of the compounds synthesized are given in Table 1.

EXPERIMENTAL

4-Methyl-2-methylcarbamoyl-1-p-nitrophenyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (IIf). When 5 g of If was suspended in concentrated hydrochloric acid, it gradually dissolved with the formation of a dark red solution. After several hours, the solution was poured into water. The orange precipitate of IIf was separated off and crystallized from ethanol to give 3.5 g of IIf.

1-p-Chlorophenyl-4-methyl-2-methylcarbamoyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (IIg). In a similar manner to the preparation of IIf, 5 g of Ig yielded 3.6 g of IIg.

2-Bromo-2-carbamoyl-1-phenyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (III). When 0.6 ml (11.4 mM) of bromine was added to a suspension of 1.2 g (3.8 mM) of IIa in 30 ml of acetic acid, the solid material dissolved. A precipitate slowly crystallized from the red solution and this was separated off and recrystallized from acetic acid, giving 1.3 g of III.

1-Phenyl-2-xanthenylcarbamoyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (IV). a) A suspension of 2 g (6.3 mM) of IIa, 1.25 g (6.3 mM) of xanthydrol, and 30 ml of acetic acid was heated in the water bath. After cooling, the dark solution deposited a yellow precipitate, which was separated off and crystallized from dimethylformamide, giving 2.1 g of IV.

b) A suspension of 2 g (6 mm) of Ia and 1.2 g (6 mM) of xanthydrol in 50 ml of acetic acid was heated in an air bath. As boiling proceeded, a precipitate was formed which was separated off. After crystallization from dimethylformamide, 1.8 g of IV was obtained.

Monoamide of α-[1-aminoind-2-en-3-on-2-yl]benzylmalonic acid (V). Two grams of IIa was added to 1N NaOH, forming, a violet-red solution. After some time, the solution became red. It was filtered and acidified. The orange precipitate was separated off and crystallized from ethanol giving 1 g of V.

α-[1-Aminoind-2-en-3-on-2-yl]benzylmalonic acid (VIa). Three grams of IIa was suspended in 1N NaOH, and the suspension was left overnight, ammonia being evolved. The resulting solution was filtered and acidified, and the red precipitate was separated off. On recrystallization, prolonged boiling had to be avoided in order to prevent possible transformation of the product. This gave 2.2 g of VIa. IR spectrum (cm^{-1}), ν_{CO} 1740, 1690, 1665; $\nu_{C=C}$ 1620; ν_{NH} 3439, 3348, 3296. The acid VIa can also be obtained by a previous procedure [14].

α-[1-Aminoind-2-en-3-on-2-yl]-p-nitrobenzylmalonic acid (VIb). As for the preparation of VIa, 2 g of IIb yielded 1.3 g of VIb.

α-[1-Aminoind-2-en-3-on-2-yl]-p-chlorobenzylmalonic acid (VIc). As for the preparation of VIa, 2 g of IIc yielded 1.2 g of VIc.

1-Phenyl-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (VIIa). This was obtained by the procedure developed earlier [14].

1-(p-Nitrophenyl)-1,2,3,4-tetrahydro-4-azafluorene-3,9-dione (VIIb). A suspension of 1 g of VIb in 30 ml of diethyleneglycol was heated at 120–130° C until the evolution of carbon dioxide had ceased. The reaction mixture became thicker. The precipitate was separated off and washed with ether. After recrystallization from ethanol, 0.3 g of VIIb was obtained.

β-[1-Aminoind-2-en-3-on-2-yl]-β-phenylpropionic acid (VIII). A suspension of 1 g of VIIa in 1N NaOH was heated in a hot water bath. A violet-red solution was formed which gradually became red. The solution was filtered and acidified, and the precipitate was separated off. After crystallization from dilute ethanol, 1.1 g of VIII was obtained.

β-[Indan-1,3-dion-2-yl]-β-phenylpropionic acid (IX). A suspension of 3 g of IIa in concentrated hydrochloric acid was boiled. The solid matter gradually became decolorized, and it was separated off and purified by recrystallization from bicarbonate solution. Crystallization from dilute acetic acid yielded 1.4 g of white crystals of IX with mp 171–173° C (according to the literature [19], mp 173° C). Compound IX was obtained in a similar manner from V, VIa, and VIII.

Ethyl β-[indan-1,3-dion-2-yl]-β-phenylpropionate (X). A few drops of concentrated H_2SO_4 was added to a suspension of 0.5 g of IX in absolute ethanol, and it was heated in the water bath. After cooling, it was poured into water and the precipitate was separated off to give 0.3 g of colorless crystals of X (mp 110–111° C, from ethanol; according to the literature [20], mp 109° C).

REFERENCES

1. Yu. E. Pelcher and G. Ya. Vanag, Izv. AN Latv. SSR, ser. khim., 45, 1964.

2. Yu. E. Pelcher and G. Ya. Vanag, Izv. AN Latv. SSR, ser. khim., 612, 1965.

3. Yu. E. Pelcher, Z. A. Bomika, and G. Ya. Vanag, Izv. AN Latv. SSR, ser. khim., 478, 1967.

4. Yu. E. Pelcher, Ya. F. Freimanis, and G. Ya. Vanag, KhGS [Chemistry of Heterocyclic Compounds], 3, 374, 1967.

5. C. K. Ingold, Structure and Mechanism in Organic Chemistry [Russian translation], IL, Moscow, p. 551, 1959.

6. G. Ya. Vanag and E. Ya. Ozol, ZhOKh, 32, 1151, 1962.

7. Yu. Ya. Silaraya, A. K. Aren, and G. Ya. Vanag, Izv. AN Latv. SSR, ser. khim., 707, 1964.

8. E. M. Danilova and V. V. Perekalin, ZhOrKh, 1, 1708, 1965.

9. H. Becker, Einführung in die Elektronentheorie organisch-chemischer Reaktionen [Russian translation], Mir, Moscow, p. 247, 1965.

10. E. I. Stankevich and G. Ya. Vanag, ZhOKh, 32, 1146, 1962.

11. Ya. F. Freimanis, in collection: Cyclic β-Diketones [in Russian], Riga, p. 218, 1961.

12. R. A. Abramovich, Giam Choo Seng, and A. D. Nation, Canad. J. Chem., 38, 761, 1960.

13. E. I. Stankevich and G. Ya. Vanag, ZhOrKh, 1, 815, 1965.

14. Ya. F. Freimanis and G. Ya. Vanag, ZhOKh, 30, 3369, 1960.

15. M. M. Shemyakin, D. N. Shigorina, A. A. Shchukina, and E. P. Semkin, Izv. AN SSSR, OKhN, 695, 1959.

16. K. Nakanishi, Infrared Absorption Spectroscopy [Russian translation], Mir, Moscow, p. 59, 1965.

17. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL, Moscow, p. 300, 1963.

18. E. I. Stankevich and G. Ya. Vanag, Izv. AN Latv. SSR, ser. khim., 84, 1963.

19. M. W. Jonescu, Bull. soc. chim. France, [4], 37, 913, 1927.

20. M. W. Jonescu and St. Secereanu, Bull. Soc., Stiinte Cluj., 3, 112, 1926; C., 1, 601, 1927.

8 August 1966

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