INVESTIGATIONS OF PYRANS AND RELATED COMPOUNDS

XLVI.* SYNTHESIS OF 4-AMINO-3-NITROCOUMARINS

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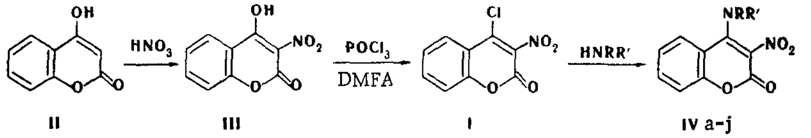
UDC 547.814.1 : 543.422.4

The action of phosphorus oxychloride in DMFA on 4-hydroxy-3-nitrocoumarin has given 4-chloro-3-nitrocoumarin, by the reaction of which with amines and ammonia 4-amino-3-nitrocoumarins have been synthesized; some of their physicochemical properties have been studied.

It has been established previously [2, 3] that the reaction of amines with 4-chlorocoumarin can form both 4-aminocoumarins and o-hydroxyphenylpropiolamides, the ratio of the reaction products depending on the nature of the amine and of the solvent used. For example, when the reaction is performed with ammonia in dimethyl sulfoxide (DMSO) solution, the reagent is directed to position 2, while under the same conditions primary and secondary amines form 4-aminocoumarins.

Continuing investigations in this direction, we have studied the reaction of ammonia and a number of amines with 4-chloro-3-nitrocoumarin (I), which was obtained in the following way:



a $R=R'=H$; b $R=H$, $R'=CH_3$, c $R=H$, $R'=n\text{-}C_4H_9$; d $R=H$, $R'=\text{tert-}C_4H_9$; e $R=H$, $R'=C_6H_5CH_2$; f $R=H$, $R'=C_6H_5$; g $R=R'=C_2H_5$; h $R=R'=n\text{-}C_3H_7$; i NRR' – piperidino; j NRR' – morpholino.

4-Hydroxy-3-nitrocoumarin (III) [4, 5] was synthesized by a modified procedure for the nitration of 4-hydroxycoumarin (II). The action on (III) of phosphorus oxychloride in DMFA solution formed (I) with a yield of 96%. The structure of (I) was confirmed by its spectra and by the subsequent chemical transformations. Its IR spectrum in chloroform had the characteristic absorption bands of a C=O group (1760 cm^{-1}), of a NO_2 group (ν_{as} 1558 and ν_s 1327 cm^{-1}), of the double bonds of a coumarin ring (1616 cm^{-1}), and of ν_{C-Cl} at 858 cm^{-1}.

The reaction of (I) with an excess of ammonia or with two moles of amine in absolute benzene solution formed the previously unreported 4-amino-3-nitrocoumarins (IVa-j) with yields of 70-100%. Under the action of dilute alkali, compounds (IV) were gradually converted into o-hydroxy-ω-nitroacetophenone (V) [4], which was also obtained by the alkaline treatment of (III). The IR spectra of compounds (IV) in chloroform have strong absorption bands in the 1720-1740-cm^{-1} region due to the vibrations of a carbonyl group and bands at 1605-1615 cm^{-1} which are characteristic for the double bonds of a coumarin ring.

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* For communication XLV, see [1].

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 885-890, July, 1973. Original article submitted July 18, 1972.

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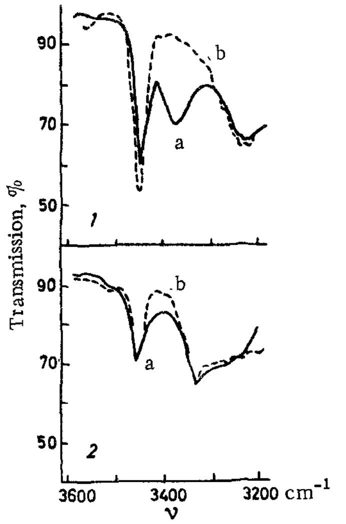


Fig. 1

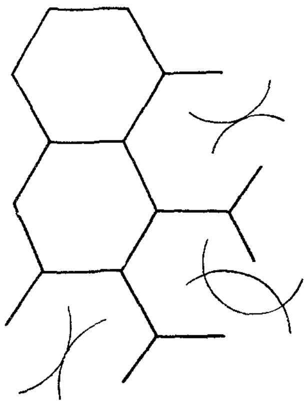


Fig. 2

Fig. 1. IR spectra in chloroform: 1) 4-n-butylamino-3-nitrocoumarin (IVc), c 0.1 M, d 1 mm (a); c 0.01 M, d 10 mm (b); 2) 4-tert-butylamino-3-nitrocoumarin (IVd), c 0.1 M, d 1 mm (a); c 0.01 M, d 10 mm (b).

Fig. 2. Sketch of the effective radii of van der Waals interaction in the molecule of 4-amino-3-nitrocoumarin (IVa).

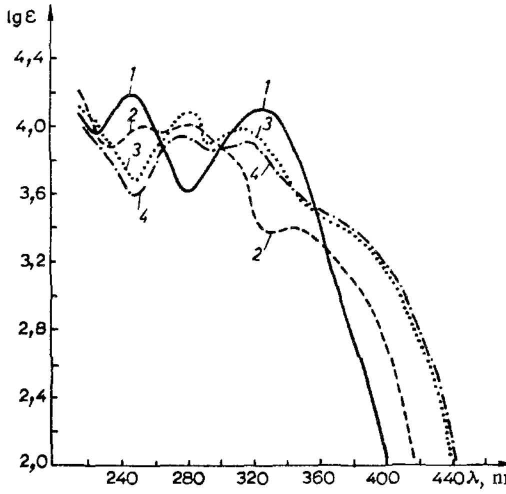
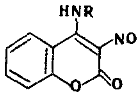
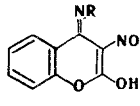


Fig. 3. UV spectra in ethanol: 1) 4-amino-3-nitrocoumarin (IVa); 2) 4-n-butylamino-3-nitrocoumarin (IVc); 3) 3-nitro-4-piperidinocoumarin (IVi), 4) 4-diethylamino-3-nitrocoumarin (IVg).

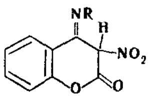
In the case of compounds (IVa-f), each containing a primary or a secondary amino group, several tautomeric forms (A-D) can be envisaged:



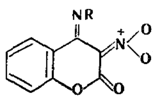
A



B



C



D

TABLE 1. UV Spectra of the 4-Amino-3-nitrocoumarins (IV)

Compound	λ_{max} (lg ε), nm
IVa	248 (4,18), 330 (4,08)
IVb	248—256 (4,20), 276—288 (4,08), 344—360 (3,33)
IVc	254—258 (3,98), 276—286 (3,99), 342—350 (3,37)
IVd	262—268 (4,11), 350—355 (3,75)
IVg	276—278 (3,94), 312—316 (3,89), 380 (3,30 inflection)
IVh	276 (4,08), 318—320 (3,98), 386—394 (3,40 inflection)
IVi	280 (4,15), 310—314 (3,96), 380 (3,30 inflection)
IVj	272 (4,19), 312 (4,11), 380—390 (3,25 inflection)

TABLE 2. 4-Amino-3-nitrocoumarins (IV)

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IVa	271—272,5[a]	$C_9H_6N_2O_4$	52,5	2,9	13,7	52,4	2,9	13,6	86
IVb	273—275[a]	$C_{10}H_8N_2O_4$	54,3	3,7	12,9	54,6	3,6	12,7	93
IVc	168—169[b]	$C_{13}H_{14}N_2O_4$	59,5	5,1	10,7	59,5	5,3	10,7	90
IVd	142—143[c]	$C_{13}H_{14}N_2O_4$	59,6	5,3	10,9	59,5	5,3	10,7	73
IVe	180—181[b]	$C_{16}H_{12}N_2O_4$	65,0	4,0	9,5	65,2	4,0	9,5	86
IVf	235—236[d]	$C_{15}H_{10}N_2O_4$	64,0	3,8	9,8	63,8	3,5	9,9	100
IVg	113—114[b]	$C_{13}H_{14}N_2O_4$	59,8	5,4	10,7	59,5	5,3	10,7	95
IVh	140—141[b]	$C_{15}H_{18}N_2O_4$	62,0	6,2	9,6	62,0	6,2	9,6	98
IVi	146—147[b]	$C_{14}H_{14}N_2O_4$	61,3	5,1	10,2	61,3	5,1	10,2	98
IVj	212—214[b]	$C_{13}H_{12}N_2O_5$	56,4	4,3	10,1	56,5	4,3	10,1	93

[a] From glacial acetic acid. [b] From absolute ethanol. [c] From a mixture of absolute benzene and hexane. [d] From a mixture of absolute acetone and absolute benzene.

On the basis of considerations according to which the α-pyrone ring of a coumarin possesses a partially aromatic nature and from an analogy with the structure of the 4-aminocoumarins [6], preference must be given to the coumarin form (A). Evidence in favor of form A was obtained by studying the PMR spectra of (IV). Thus, in the spectrum of (IVc) in $CDCl_3$ the signals of the protons of the $N-CH_2$ group appear at 3.8 ppm in the form of a quadruplet through spin–spin coupling ($J \approx 6$ Hz) with the protons of the neighboring methylene group and with the proton attached to the nitrogen atom, the broad signal of which is located in the 9.8-ppm region. On the addition of CD_3OD, this quadruplet is converted into a triplet and the signal at 9.8 ppm practically disappears.

Compounds (IVa-f) can form both intermolecular (the hydrogen of the amino group with the oxygen of the nitro or of the carbonyl group) and intramolecular (the hydrogen of the amino group with the oxygen of the nitro group) hydrogen bonds, in the same way as 2-nitroaniline [7, 8] and 1-amino-2-nitronaphthalene [9, 10]. The two types of hydrogen bond are shown particularly clearly in the IR spectra of (IVc) – the stretching vibrations of a free NH group with a frequency of 3450 cm^{-1} can be seen together with the vibrations of a bound NH group at 3360 and 3240 cm^{-1}. With dilution, the broad band at 3240 cm^{-1} does not change (intramolecular hydrogen bond) and the band at 3360 cm^{-1} disappears (intermolecular hydrogen bond), while the intensity of the band at 3450 cm^{-1} increases (Fig. 1). In the spectra of (IVd) and (IVf) [for (IVd) see Fig. 1], the vibrations ν_{NH} appear only in the form of two bands: 3440 cm^{-1} (free NH) and 3240-3330 cm^{-1} (broad band, obviously of NH participating in an intramolecular hydrogen bond), the positions and intensities of which do not change on dilution. Because of the low solubility of (IVa, b, e) in the usual organic solvents it was not possible to follow the behavior of their ν_{NH} bands in the 3200-3500-cm^{-1} region.

Some features of the spectral characteristics of compounds (IV) must be explained by the assumption that the nitro and amino groups cannot be located simultaneously in the plane of the coumarin ring (there is no doubt that in this system there is a tendency for the nitro and amino groups to be located in the same plane as the pyrone ring as the result of the conjugation effect). From the sketch of the effective radii of van der Waals interactions in the molecule of (IVa) (Fig. 2) it can be seen that the hydrogen atom of the amino group and the oxygen of the nitro group undergo strong mutual repulsion if they have a coplanar arrangement. At the same time, the hydrogen atom of the amino group and the hydrogen atom in the peri position (i.e., at C_5) are sterically freer. It follows from this that in a compound (IV) with a secondary amino group the substituent of the amino group must undergo greater repulsion from the side of the nitro group than from the hydrogen atom at C_5. Consequently, in those molecules of compounds (IV) with secondary amino groups in which there are no intramolecular hydrogen bonds the substituents on the nitrogens occupy the positions remote from the nitro groups while the coplanarity of the amino groups with the coumarin rings will nevertheless not be achieved because of repulsion from the rigidly bound peri hydrogen atoms. Where there is an intramolecular hydrogen bond between the nitro and secondary amino groups the noncoplanarity of the arrangement of the amino group entails departure from the plane of conjugation of the nitro group, as well, since otherwise the most favorable conditions for the formation of a hydrogen bond will not be ensured.

If the amino group of a compound (IV) is tertiary (with the same substituents, R and R', as in our case), the angle of departure of the amino and (or) the nitro group from the plane of the coumarin ring will be determined mainly by the spatial repulsion between a substituent in the amino group and the nitro group.

A disturbance of the coplanarity of the nitro group—α-pyrone ring system must be accompanied by a decrease in the relative and absolute intensities of ν_S of the vibrations of the nitro group, as is the case in a number of unsaturated cyclic and acyclic nitro compounds [11, 12].

It must be assumed that the nitro group in a compound (IV) with a tertiary amino group departs from conjugation with the double bond of the pyrone ring to a smaller extent than in a compound (IV) with an intramolecular hydrogen bond. Thus, in the spectrum of (IVc) the intensity of the 1327-cm^{-1} band is only 100 ε units (mole^{-1} · cm^{-1} · liter), while in the spectra of (IVg, h, and j) the ε values of the bands at 1313, 1315, and 1308 cm^{-1} are, respectively, 220, 226, and 331 ε units and approximate to the intensities of the bands at 1327 cm^{-1} in compounds (I) and (III) (331 and 161 ε units, respectively). The integral intensities of the 1327-cm^{-1} bands of compounds (III) and (IVg), equal to 1.06 and 1.08 practical units (10^{-4} mole^{-1} · cm^{-2} · liter) also exceed those for the ν_S bands in the spectra of (IVc, d) (0.66 and 0.55 unit, respectively), although they are less than the intensities of the bands of similarly substituted benzene (1.8 and 1.98 units for the 1332- and 1345-cm^{-1} bands in o-nitrophenol and o-nitroaniline, respectively [8]). The latter circumstance is due not only to the impossibility of the formation of a completely coplanar nitro group—α-pyrone ring system in compounds (I), (III), and (IVa, g-j) (Fig. 2) but also, probably, to features of the structure of the benzopyrone ring.

The UV spectra (Fig. 3, Table 1) of compounds (IVa-f) with primary or secondary amino groups differ considerably from the UV spectra of compounds (IVg-j) with tertiary amino groups, which is obviously due to a change in the electronic interaction of the amino and nitro groups with one another and with the π-electronic system of the coumarin ring, and also, possibly, to a difference in their solvation, as is the case, for example, in a series of mono- and dialkylaminovinyl ketones of indene systems [13]. In actual fact, the intensities of the main absorption bands of (IVa) (248 and 330 nm) are the highest (ε 15,000 and 12,000, respectively) when the probability of a planar arrangement of the NH_2 and NO_2 groups is highest (Fig. 3, curve 1). The introduction of alkyl substituents into the amino group leads to an approach of the main bands to one another and to the appearance of a bathochromic band (360-380 nm), which is responsible for the intense coloration of (IVb-j). Compounds (IVb-j) form two types of absorption curves. The first type of curve corresponds to compounds with a secondary amino group (Fig. 3, curve 2) and is characterized, in comparison with (IVa), by a bathochromic inflection of the curve in the visible region (~350 nm) and by a weak hypsochromic shift of the "center of gravity" of the most intense absorption bands (~10 nm). The second type of absorption curve is formed by compounds with a tertiary amino group (Fig. 3, curves 3 and 4). In this case a bathochromic shift of the center of the strong bands (~20 nm) and of the long-wave inflection on the absorption curve (~23 nm) is observed.

EXPERIMENTAL

The UV spectra were taken on an SF-4 spectrophotometer in ethanol at 1 · 10^{-5}-1 · 10^{-4} M, and the IR spectra on a UR-10 instrument. The PMR spectra (in the δ scale) were obtained on a Varian T-60 instrument.

4-Hydroxy-3-nitrocoumarin (III). With stirring at 20°C (water cooling), a mixture of 17.6 g (0.2 mole) of 72% nitric acid and 20 g (0.2 mole) of concentrated sulfuric acid was added dropwise to a suspension of 32.4 g (0.2 mole) of (II) in 100 ml of glacial acetic acid, and the mixture was stirred for 4-5 h and poured into 300 ml of cold water. The precipitate was filtered off and washed with water, giving 34.4 g (86%) of (III), mp 169-170°C (from absolute ethanol). The substance was identical with a sample obtained by a published method [4].

4-Chloro-3-nitrocoumarin (I). With cooling and stirring, 15.3 g (0.1 mole) of phosphorus oxychloride was added to 7.3 (0.1 mole) of absolute DMFA, and the mixture was stirred at 20°C for 15 min, and then a solution of 20.7 g (0.1 mole) of (III) in 50 ml of absolute DMFA was added dropwise. The mixture was stirred for 15 min and was diluted with 50 ml of cold water. The precipitate was filtered off and was washed with a saturated solution of $NaHCO_3$ and with water to give 21.6 g (96%) of (I), mp 162-163°C (from a mixture of absolute benzene and hexane). Found, %: C 47.9; H 1.9; Cl 15.5; N 6.2. $C_9H_4ClNO_4$. Calculated, %: C 47.9; H 1.8; Cl 15.7; N 6.2. IR spectrum, cm^{-1}: 1754 (C=O), 1613 (C=C bond of the coumarin ring), 1554 and 1327 (NO_2).

The 4-Amino-3-nitrocoumarins (IVa-j). a) With stirring, 0.04 mole of the appropriate amine was added dropwise to a solution of 4.4 g (0.02 mole) of (I) in 60 ml of absolute benzene, the mixture was stirred at 20°C for 1 h, and the precipitate was filtered off and was washed with benzene and, repeatedly, with water. The benzene solution was washed with 1% hydrochloric acid and with water and was evaporated, giving additional amounts of the compound (IV). Compounds (IVg-i), which are readily soluble in benzene, were isolated from the benzene solution after similar treatment.

b) A current of dry ammonia was passed for 30 min through a solution of 4.4 g (0.02 mole) of (I) in 60 ml of absolute benzene. The precipitate that separated out was filtered off and was repeatedly washed with water. Information on the compounds (IV) obtained is given in Table 2. IR spectra of (IVa), cm^{-1}: in the crystalline state – 3400 s, 3330 s, 3250-3220 m, 3120 w, 3080 w, 3040 w, 1720 s, 1636 s, 1615 s, 1545 m, 1450 m, 1331 m, 1300 s, 1277 m, 1220 w, 1108 m, 905 m, 769 s; in DMSO – 1725 s, 1640 m, 1617 s, 1550 m, IR spectrum of 4-dideuteroamino-3-nitrocoumarin (in DMSO), cm^{-1}: 1725, 1615, 1565.

o-Hydroxy-ω-nitroacetophenone (V). a) A solution of 2.07 g of (III) in 20 ml of 5% caustic soda was kept at 20°C for 24 h and was then filtered and acidified with 10% hydrochloric acid. The precipitate was filtered off and washed with water to give 1.56 g (86%) of (V), mp 108.5°C (from 70% ethanol) [4].

b) A suspension of 2.5 mmoles of (IVa), (IVg), or (IVi) in 5 ml of 5% caustic soda was kept at 20°C until the respective compound (IV) had dissolved completely (5 h and 3 and 7 days, respectively), and was then worked up similarly, giving (V) with yields of 81, 91, and 78%, respectively.

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