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CONDENSATION OF 1-AMINOISOINDOLE WITH 2-CARBETHOXYCYCLOPENTANONE AND 2-CARBETHOXYCYCLOHEXANONE

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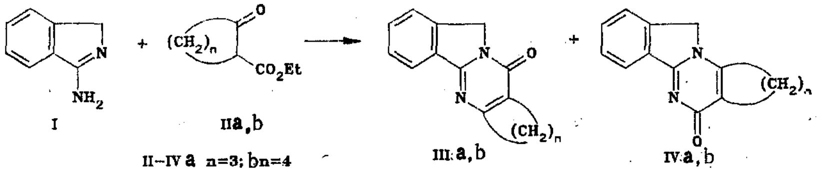
The condensation of 1-aminoisoindole with 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone was studied. The conditions for the isolation of the resulting isomers were selected. The structures of the synthesized substances were proved by means of PMR spectroscopy with the aid of shift reagents.

Continuing our research on the development of methods for the preparation of condensed isoindoles [1], we studied the condensation of 1-aminoisoindole (I) with 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone (IIa, b). It was previously shown [2, 3] that of two possible isomeric compounds, only pyrimido[2,1-a]isoindol-4(6H)-one derivatives are formed in the condensation of I with ethyl acetoacetate and aroylacetates.

β-Keto esters IIa, b do not react with aminoisoindole hydrochloride; however, the addition of an equivalent of sodium ethoxide to the indicate mixture makes it possible to isolate a solid reaction product, which, according to the results of thin-layer chromatography (TLC), contains two substances with different chromatographic mobilities; the starting mixture always contains a somewhat greater amount of the chromatographically more mobile substance.



I
IIa,b
II–IV a n=3; b n=4
IIIa,b
IVa,b

We were able to select experimental conditions under which the resulting mixture can be separated into individual III and IV, which have different melting points and, as demonstrated by elementary analysis, are isomers. The PMR spectra of the isomers recorded in trifluoroacetic acid confirm the pyrimido[2,1-a]isoindole structure proposed for them but do not make it possible to arrive at a conclusion as to the structure (III or IV) that should be assigned to the products. For the rigorous proof of the structures of the synthesized compounds we applied the shift reagent method using europium (III) 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctanedion-4,6-ate [$Eu(FOD)_3$] as the lanthanide shift reagent (LSR). Compounds III and IV have two centers for coordination with the LSR, viz., the carbonyl oxygen atom and the $N_{(1)}$ atom of the pyrimidine ring. Since $Eu(FOD)_3$ is a sterically hindered Lewis acid, one might expect that coordination of europium will occur only at the carbonyl oxygen atom, since the hydrogen atom attached to the $C_{(10)}$ atom and any substituent in the 2 position (even the carbonyl group in structure IV) will create steric hindrance to coordination with the LSR at the nitrogen atom [4].

The lanthanide-induced shifts (LIS) for the proton signals of isomers IIIa-IVa and IIIb-IVb should differ substantially: in the case of compounds with structure III the maximum LIS are expected for the signals of the protons of the methylene group of the isoindoline ring and

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TABLE 1. Characteristics of the Absorption Bands in the Electronic Spectra of IIIa, b and IVa, b in Methanol[a]

Compound	λ_{max}, nm (lg ε)
IIIa	206 (4,5), 243 (4,0), 264 (3,8)[b], 290 (3,9)[b], 303 (4,0), 312 (3,9)[b], 327 (3,6)[b]
IIIb	205 (4,5), 243 (4,0), 264 (3,8)[b], 288 (3,9)[b], 300 (4,0), 311 (3,9)[b], 325 (3,6)[b]
IVa	208 (4,4), 238 (4,4)[b], 245 (4,5), 278 (3,9)[b], 288 (3,8)[b]
IVb	208 (4,4), 238 (4,4)[b], 245 (4,5), 277 (3,9)[b], 288 (3,8)[b]

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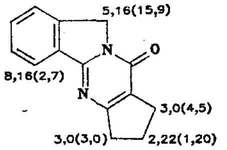
[a] Compounds IVa, b have one minimum at 224 nm (4.0), and IIIa, b have two minima at 230 (3.8) and 272 nm (3.8), respectively.
[b] Inflection of the absorption curve.

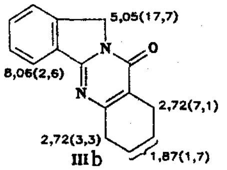
one of the methylene groups of the cyclopentene (cyclohexene) ring, since precisly these groups are closer to the coordination center of these molecules. In the case of alternative structures IV the LIS of the signal of the methylene group of the isoindoline ring should be significantly smaller than the LIS of one of the methylene groups of the cyclopentene or cyclohexene ring.

Of the two pairs of isomers, only the low-melting and chromatographically more mobile compounds have the ability to dissolve in deuterochloroform in the necessary concentrations. Significant paramagnetic shifts of the signals of all of the protons occur when the LSR is added to solutions of these compounds; the greatest LIS are observed for the signal of the methylene protons of the isoindoline ring.

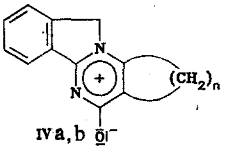
The chemical shifts of IIIa, b and (in parentheses) the chemical shifts induced by the LSR are presented below:



IIIa



IIIb



IVa,b

Thus structures IIIa and IIIb apparently correspond to these isomers. To confirm this conclusion we calculated the geometrical structure of the adducts of the LSR with IIIa, b. The calculated length of the O—Eu bond was found to be 2.2-2.3 Å. These bond lengths are in complete agreement with the data on the geometry of the adducts of the LSR with other compounds [5] that contain a carbonyl group as the LSR coordination center. Thus the chromatographically more mobile isomers, which have lower melting points, have pyrimido[2,1-a]isoindol-4(6H)-one structure IIIa, b, and we assign the alternative pyrimido[2,1-a]isoindol-2(6H)-one structure IVa, b to the less chromatographically mobile isomers, which have higher melting points.

The characteristics of the electronic and IR spectra of the isomeric structures are presented in Tables 1 and 2. Data from a comparative analysis of the properties of isomeric systems that can be used in structural investigations of other subjects are rarely presented in the literature. It is therefore important to point out the fundamental differences in the IIIa, b and IVa, b structures. The compounds with the IIIa, b structure absorb in the longer-wave part of the spectrum than the compounds with the IVa, b structure and have three clearly expressed absorption bands. The contour of the absorption curve of IVa, b is more complex: there are four bands, and the long-wave band with a maximum at 300 nm displays a weakly developed vibration structure. The absence of carbonyl absorption and difficulty in the identification of the stretching vibration of the C═N bond in structures IVa, b are peculiarities of the IR spectra of the isomeric structures; in our opinion, this is associated with significant polarization of the carbonyl group and the large contribution of a mesomeric structure of the V type. Dipolar structures of this type for IIIa, b eivdently play a smaller role, since the stretching vibrations of the C═O and C═N bonds show up more distinctly for them (see Table 2).

TABLE 2. IR Spectra of IIIa, b and IVa, b[a]

Compound	νC—H	δC—H	Stretching vibrations of the multiple bonds and the ring system
IIIa	2960 (66) 2910 (76) 2860 (79)	735 (58) 760 (35)	1673 (1), 1595 (33)[b], 1465 (52) 1650 (46)[c], 1580 (37)[d], 1440 (57) 1525 (2), 1430 (69)
IIIb	2930 (55) 2870 (72)	730 (62) 760 (32)	1670 (1), 1585 (45)[b] 1465 (59) 1650 (15); 1540 (29)[d], 1442 (60) 1605 (5), 1435 (60)
IVa	2930 (76) 2860 (81)	753 (76) 783 (61) 810 (74)	1640 (28), 1545 (10)[d], 1490 (35) 1625 (5), 1470 (50) 1605 (1), 1446 (72), 1438 (73)
IVb	2940 (66) 2870 (78)	750 (75) 780 (58) 800 (75)	1635 (33), 1545 (3)[d], 1480 (27) 1620 (35), 1465 (50)[c], 1602 (1), 1450 (66), 1435 (67)

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[a] The frequencies of the vibrations in reciprocal centimeters are presented; the intensities in percent transmission are given in parentheses. [b] $\nu_{C=O}$. [c] Inflection. [d] ν_{CN}.

EXPERIMENTAL

The melting points were corrected and were measured with a Boetius apparatus (East Germany). The individuality of the substances was verified by thin layer chromatography (TLC) on Silufol plates by elution with chloroform—methanol (95:5). The UV spectra of $5 \cdot 10^{-5}$ M solutions of the substances in alcohol were recorded with a Specord UV-vis spectrometer (East Germany). The IR spectra of KBr pellets were recorded with a Pye—Unicam SP-300 spectrometer. The PMR spectra of solutions in $CDCl_3$ and trifluoroacetic acid were measured with a ZKP-60 spectrometer (East Germany) with an operating frequency of 60 MHz at 25°C with tetramethylsilane (TMS) as the internal standard. In the experiments with the LSR $Eu(FOD)_3$ was added successively in portions to a 0.1 M solution of the base in $CDCl_3$, and the PMR spectrum was recorded each time. The specific induced shifts of the corresponding signals were obtained by extrapolating the linear sections of the dependence of the induced shifts on the $Eu(FOD)_3$: base ratio to 1:1.

1-Aminoisoindole was obtained in low yield by the method in [6]. 2-Carbethoxycyclopentanone was synthesized by the method in [7], and 2-carbethoxycyclohexanone was synthesized by the method in [8].

Condensation of 1-Aminoisoindole with 2-Carbethoxycyclopentanone. A solution of 2.3 g (0.1 mole) of sodium in 16 ml of absolute alcohol was added to a mixture of 16.8 g (0.1 mole) of the hydrochloride of I and 17.2 g (0.11 mole) of 2-carbethoxycyclopentanone in 50 ml of absolute alcohol, and the reaction mixture was refluxed for 3 h. Water (70 ml) was added, and the precipitated crystals were removed by filtration. The precipitate was washed thoroughly with water and air dried to give 18.1 g (81%) of a gray crystalline product, which, according to the results of TLC, was a mixture of two substances with R_f 0.5 (58%) and R_f 0.14 (17%).

3,4-Trimethylenepyrimido[2,1-a]isoindol-2(6H)-one (IVa). An 18-g sample of the substance from the preceding experiment was refluxed for 3 min in 100 ml of benzene in a flask equipped with a reflux condenser, after which the undissolved residue was crystallized from dimethylformamide (DMF) to give 6.5 g (29%) of colorless crystals with R_f 0.14 and mp 301-303°C. PMR spectrum (CF_3CO_2H): 5.55 (2H, s, 6-CH_2), 7.92 (3H, center of a multiplet, 7,8,9-H), and 8.30 ppm (1H, d, 10-H, J = 7 Hz). Found: C 75.1; H 5.3; N 12.4%. $C_{14}H_{12}N_2O$. Calculated: C 74.9; H 5.4; N 12.5%.

2,3-Trimethylenepyrimido[2,1-a]isoindol-4(6H)-one (IIIa). The benzene solution from the preceding experiment was evaporated at reduced pressure, and the residue was crystallized from isopropyl alcohol to give 13 g (58%) of colorless crystals with Rf 0.55 and mp 231-233°C. PMR spectrum (CF_3CO_2H): 5.55 (2H, s, 6-CH_2), 7.95 (3H, center of a multiplet, 7,8,9-H), and 8.26 ppm (1H, d, 10-H, J = 7 Hz). Found: C 75.3; H 5.4; N 12.6%. $C_{14}H_{12}N_2O$. Calculated: C 74.9; H 5.4; N 12.5%.

3,4-Tetramethylenepyrimido[2,1-a]isoindol-2(6H)-one (IVb). This compound was obtained in 17% yield from 0.1 mole of the hydrochloride of I and 0.11 mole of 2-carbethoxycyclohexanone by a procedure similar to that used to prepare IVa. The colorless crystals had mp 292-295°C (from DMF) and R_f 0.17. PMR spectrum (CF_3CO_2H): 5.49 (2H, s, 6-CH_2), 7.89 (3H, center of a multiplet, 7,8,9-H), and 8.30 ppm (1H, d, 10-H, J = 7.5 Hz). Found C 75.5; H 5.8; N 11.7%. $C_{15}H_{14}N_2O$. Calculated: C 75.6; H 5.9; N 11.7%.

2,3-Tetramethylenepyrimido[2,1-a]isoindol-4(6H)-one (IIIb). This compound was obtained in 56% yield from 0.1 mole of the hydrochloride of I and 0.11 mole of 2-carbethoxycyclohexanone by a procedure similar to that used to prepare IIIa. The product had mp 212-213°C (from isopropyl alcohol) and R_f 0.61. PMR spectrum (CF_3CO_2H): 5.48 (2H, s, 6-CH_2), 7.90 (3H, center of a multiplet, 7,8,9-H), and 8.30 ppm (1H, d, 10-H, J = 7.5 Hz). Found: C 75.7; H 5.93; N 12.1%. $C_{15}H_{14}N_2O$. Calculated: C 75.6; H 5.92; N 11.7%.

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