RESEARCH ON BENZ[c,d]INDOLIN-2-ONE DERIVATIVES.
BROMINATION OF BENZ[c,d]INDOLIN-2-ONECARBOXYLIC ACIDS

G. I. Bystritskii, G. N. Rodionova,
S. V. Eletskaya, G. V. Sheban,
G. N. Vorozhtsov, B. E. Zaitsev,
and N. A. Partalla

UDC 547.756'657:542.944.1

It was experimentally observed that electrophilic substitution in, respectively, the 6 and 8 positions or the 8 position occurs when a carboxy group is present in the peri positions (in the 5 or 6 position) of benz[c,d]indolin-2-one. When two carboxy groups are simultaneously present in the 5 and 6 positions or when there is one carboxy group in the 6 position and a bromo substituent in the 5 position, the carboxy group is readily replaced by bromine. The electronic structures and reactivities of benz[c,d]indolin-2-one derivatives were investigated by spectroscopy and quantum chemistry.

The ease of replacement of one carboxy group by bromine was previously noted in a study of the bromination [1] of peri-substituted naphthalic acids, particularly benz[c,d]indolin-2-one-5,6-dicarboxylic acid. It was shown that the carboxy group in the para position relative to the nitrogen atom is replaced by bromine and that the second carboxy group is not involved even when the reaction is carried out with excess bromine. In this case further bromination takes place in the 8 position to give 6,8-dibromobenz[c,d]indolin-2-one-5-carboxylic acid.

It was natural to assume that this somewhat unusual trend of bromination reactions was associated with the effect of the second carboxy group in the peri position.

In connection with the material set forth above, it was of interest to ascertain the effect of some other substituent in the 5 position in place of the carboxy group on the bromination. With the end in mind, we carried out the bromination of 5-bromobenz[c,d]indolin-2-one-6-carboxylic acid (I), the synthesis of which was previously described in [2].

The reaction was carried out by refluxing in acetic acid with an equimolar amount of bromine. As a result, 5,6-dibromobenz[c,d]indolin-2-one (II) is formed as the principal product without admixed 8-bromo derivative, and 5,6,8-tribromobenz[c,d]indolin-2-one (III) is formed upon further bromination, i.e., the incorporation of bromine in the 8 position occurs only after replacement of the carboxy group in the 6 position, even though it was difficult to anticipate such an unambiguous course of the reaction, considering the ease of bromination in the 8 position of benz[c,d]indolin-2-one.

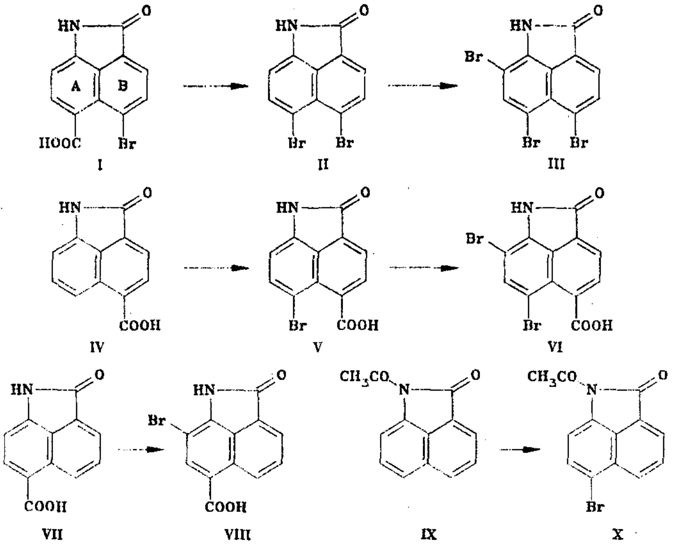
In order to confirm the effect of a peri substituent we carried out the bromination of 5- and 6-monocarboxybenz[c,d]indolin-2-ones. In this case bromination proceeded in the same way as other electrophilic substitution reactions; in benz[c,d]indolin-2-one bromination occurred in the para and ortho positions relative to the NH group [1]. 6-Bromobenz[c,d]indolin-2-one-5-carboxylic acid (V) and 6,8-dibromobenz[c,d]indolin-2-one-5-carboxylic acid (VI), respectively, were obtained from benz[c,d]indolin-2-one-5-carboxylic acid (IV), whereas only 8-bromobenz[c,d]indolin-2-one-6-carboxylic acid (VIII) was obtained from benz[c,d]indolin-2-one-6-carboxylic acid (VII). Compounds that do not contain carboxy groups were not observed in the reaction products in either case.

The IR spectra of the substances obtained are characterized by absorption bands of stretching vibrations of N—C=O (1726 cm^{-1}), COOH (1666-1673 cm^{-1}), and $COCH_3$ (1693 cm^{-1}) groups and by absorption bands of out-of-plane deformation vibrations of neighboring 2-, 3-, 7-, and 8-H atoms at 860, 760, and 733 cm^{-1} and an isolated 6-H atom at 900-926 cm^{-1}.

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1363-1367, October, 1985. Original article submitted July 10, 1984; revision submitted January 14, 1985.

0009-3122/85/2110-1117$09.50

In the PMR spectrum of naphthostyril the multiplets of the 6-, 7-, and 8-H protons are situated at stronger field (7.2-7.8 ppm) under the influence of the heteroring nitrogen atom than the multiplets of the 2-, 3-, and 4-H protons (7.8-8.4 ppm). Replacement of the 5-, 6-, or 8-H proton by bromine eliminates the multiplicity and shifts the signals of the remaining protons of this ring to weak field.



The results show quite validly that the presence of a bulky substituent in the peri position relative to the carboxy group is necessary for bromination with replacement of the carboxy group by bromine. This is necessary but not sufficient. As we have already noted above, the overall electronic structure of the molecule has an undoubted effect. Thus, whereas the carboxy group in the 6 position in I is readily replaced by bromine, in the isomeric V bromination takes place in the 8 position without involving the carboxy group even under considerably more severe conditions and in the presence of excess bromine. This is also indicated by the fact that we were completely unable to carry out the bromination of naphthalene-1,4,5-tricarboxylic acid; the reaction also does not occur with naphthalic acid under the same conditions, although in these cases we have peri-oriented bulky substituents.

Acetylation of benz[c,d]indolin-2-one at the nitrogen atom deactivates the molecule appreciably. In the bromination of N-acetylbenz[c,d]indolin-2-one (IX) [3] we were able to obtain only 6-bromo-N-acetylbenz[c,d]indolin-2-one (X), and a dibromo-substituted compound was not detected even when the reaction was carried out with excess bromine.

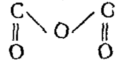
In order to explain the occurrence of the reactions indicated above we calculated the molecular diagrams, electronic absorption spectra, and the reactivity indexes, viz., the energies of localization of electrophilic substitution (L_t-) and the electron densities in the boundary orbitals [highest occupied molecular orbitals (HOMO)] (f_t-) (Table 1).

The quantum-chemical calculations were carried out by the Pariser—Parr—Pople (PPP) method within the approximation of a variable β value with optimization of the geometry of the ground state with respect to the minimum of the atomization energy [7, 8]. The calculations of the ground and excited states of the molecules were made with an M-220-M computer by means of a modified program, the algorithm of which was described in [9]. In the calculation of the excited states the configuration interaction matrix consisted to 25 singly excited configurations. The correctness of the calculations is confirmed by the satisfactory agreement between the parameters of the experimental and calculated spectra (Fig. 1). Because of the lack of reliable parameters for the Br atom, calculations of the bromo-substituted molecules were not made.

The closeness of the electronic absorption spectra of the investigated molecules in the case of bromination in ethanol and acetic acid — the reaction medium — makes it possible to assume that the unprotonated molecule in the lactam form undergoes the reaction.

It is apparent from Table 1 that, according to the L_t- and f_t- values, electrophilic substitution in benz[c,d]indolin-2-one should take place readily in the 6 position and then in the 8 position. The remaining positions are deactivated significantly. The energies of electrophilic localization for the 6 and 8 positions decrease somewhat when there is a carboxy

TABLE 1. Energies of Localization of Electrophilic Substitution (L_{t^-}), Densities of the Boundary Electrons (for the HOMO) (f_{t^-}), and Charges on the Atoms (Q_t) of Benz[c,d]indolin-2-one Derivatives

Compound	Substituent in position			L_t^-, eV, position						f_t^-, position						Q_t, position						
	1	5	6	3	4	5	6	7	8	3	4	5	6	7	8	3	4	5	6	7	8	1
XIV	H	H	H	7,67	7,83	6,27	2,81	7,60	4,90	0,076	0,066	0,159	0,366	0,080	0,240	0,061	0	0,029	−0,011	0,006	−0,038	0,304
IV	H	COOH	H	7,82	8,07	7,25	2,78	7,65	4,35	0,051	0,037	0,086	0,351	0,062	0,258	0,052	0	0,004	0,019	0,010	−0,040	0,404
VII	H	H	COOH	7,72	7,66	5,90	3,40	7,79	5,19	0,076	0,080	0,184	0,332	0,072	0,228	0,068	0,003	0,065	−0,037	0,006	−0,049	0,307
IX	$COCH_3$	H	H	7,74	8,01	6,0	3,61	7,65	5,93	0,090	0,074	0,193	0,336	0,095	0,198	0,064	0,006	0,028	0,002	0,006	−0,032	0,349
XII	$COCH_3$	H	COOH	7,81	7,76	5,56	4,27	7,85	6,15	0,088	0,091	0,222	0,300	0,086	0,186	0,07	0,009	0,063	−0,023	0,005	0,043	0,350
XI	$COCH_3$	COOH	COOH	8,06	8,06	5,45	4,93	8,43	6,31	0,087	0,087	0,242	0,276	0,066	0,192	0,076	0,080	0,011	−0,043	0,002	−0,046	0,351
XIII	H	 $C(=O)-O-C(=O)$		8,05	8,66	6,77	3,33	8,51	5,46	0,08	0,044	0,156	0,362	0,054	0,236	0,059	0,069	−0,020	−0,059	0,076	−0,040	0,310

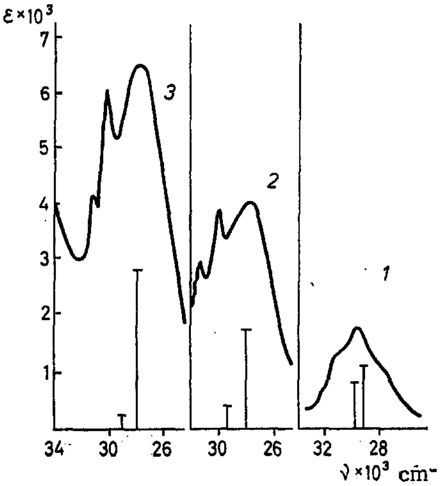


Fig. 1. Electronic absorption spectra (the vertical lines are the calculated spectra): 1) N-acetylbenz[c,d]indolin-2-one; 2) benz-[c,d]indolin-2-one; 3) benz[c,d]indolin-2-one-5-carboxylic acid.

group in the 5 position. The electron densities in the boundary orbitals (HOMO) for benz[c,d]-indole-2-one-5-carboxylic acid also indicate the high probability of electrophilic substitution as in the case of XIV.

According to the L_t- and f_t- values, similar character of electrophilic substitution should be observed for the VII molecule: $L_{8^-}/L_{6^-} \approx 1.5$, which confirms the experimental data on the decrease in the reactivity of the 8 position in this compound.

According to the L_t- values, the addition of an acetyl group to the nitrogen atom of the benz[c,d]indolin-2-one molecule of IX, substitution at the most reactive 6 and 8 centers; this is confirmed by an analysis of the f_t- values. It should be noted that the character of electrophilic substitution for the benz[c,d]indolin-2-one-5,6-dicarboxylic acid molecule in anhydride form XIII is similar to that of the VII molecule [1].

In a number of cases the π charges on the nitrogen and carbon atoms (Q_t) are in agreement with the experimental data on electrophilic reactions in the investigated series of compounds (Table 1). Thus substitution, which does not contradict the L_t- and f_t- values, is predicted in the case of IV, but the 8 position proves to be the most preferred position for the remaining compounds.

Thus, it may be concluded that the reactivities of benz[c,d]indolin-2-one and its derivatives in electrophilic substitution reactions are satisfactorily described by the energies of electrophilic localization in conformity with the Wheland model of the transition state. The f_t- values correctly predict the directions of electrophilic substitution in the 6 and 8 positions but do not explain the effect of the acetyl group attached to the nitrogen atom on the overall decrease in the reactivity. At the same time, the π charges on the atoms correlate slightly with the reactivities of the molecules.

It has been previously shown [4-6] that retention of an almost constant value of the maximum of the long-wave band and a pronounced change in the intensity of this band as a function of the type and position of the substituents are observed in the electronic absorption spectra of benz[c,d]indolin-2-one. The calculations made it possible to make a more detailed assignment of the bands in the spectra of the investigated compounds. According to the calculations, 81% of the long-wave band in the spectrum of benz[c,d]indolin-2-one is related to transition from the HOMO (ψ_n) to the lowest vacant molecular orbital (ψ_m). The transition is polarized at an angle of 80° relative to the long axis. The nitrogen atom and the A ring act as the electron-donor fragment in this transition, and the principal electron acceptor is the B ring.

EXPERIMENTAL

The electronic absorption spectra of solutions of the compounds (c $4 \cdot 10^{-2}$ g/liter) were recorded with a Specord UV-vis spectrophotometer under standard conditions in quartz cuvettes with an absorbing-layer thickness of 1 cm.

The IR spectra of KBr pellets were obtained with a Specord IR-75 spectrometer. The PMR spectra of solutions in CF_3COOH were recorded with a Bruker WP-80/CW spectrometer with hexamethyldisiloxane as the internal standard.

5,6-Dibromobenz[c,d]indolin-2-one (II). A mixture of 1.0 g of acid I, 20 ml of glacial acetic acid, and 0.55 g of bromine was refluxed for 1 h, after which it was poured into 60 ml of water, and the precipitate was removed by filtration, washed, and dried to give II with mp 288-289°C (from ethanol). Found: C 40.6; H 1.6; Br 49.1; N 4.1%. $C_{11}H_5Br_2NO$. Calculated: C 40.4; H 1.5; Br 48.9; N 4.3%. IR Spectrum: 1726, 1633, 1280, 1113, 860, 760, and 730 cm^{-1}. PMR spectrum: 8.0 (t, 7-H, 8-H), 8.35 (d, 2-H, 3-H), and 9.8 ppm (s, NH).

5,6,8-Tribromobenz[c,d]indolin-2-one (III). A mixture of 0.5 g acid I, 10 ml of glacial acetic acid, and 0.9 g of bromine was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, and dried to give 0.6 g of III with mp 294-295°C (from acetic acid). Found: Br 57.9; N 3.5%. $C_{11}H_4Br_3NO$. Calculated: Br 59.1; N 3.4%. IR spectrum: 1720, 1633, 1280, 1115, 926, 853, and 726 cm^{-1}. PMR spectrum: 8.28 (s, 7-H-, 8.33 (d, 3-H), 8.44 (s, 2-Hm, and 9.80 ppm (broad s, NH).

6-Bromobenz[c,d]indolin-2-one-5-carboxylic Acid (V). A mixture of 0.6 g of acid IV, 20 ml of acetic acid, and 0.45 g of bromine was refluxed for 1 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, and dried to give 0.54 g of V with mp 301-302°C (from acetic acid). Found: C 49.1; H 2.3; Br 27.3; N 4.4%. $C_{12}H_6BrNO_3$. Calculated: C 49.3; H 2.1; Br 27.4; N 4.8%. IR spectrum: 1726, 1666, 1633, 1280, 1115, 860, 760, and 733 cm^{-1}. PMR spectrum: 8.0 (t, 7-H, 8-H), 8.4 (d, 2-H, 3-H), and 9.8 ppm (broad s, NH).

6.8-Dibromobenz[c,d]indolin-2-one-5-carboxylic Acid (VI). A mixture of 0.3 g of acid IV, 20 ml of acetic acid, and 0.45 g of bromine was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration, washed and dried to give 0.46 of VI with mp 360°C (from acetic acid). Found: C 38.3; H 1.4; Br 42.8; N 3.5%. $C_{12}H_5Br_2NO_3$. Calculated: C 38.8; H 1.4; Br 43.1; N 3.8%. IR Spectrum: 1720, 1673, 1633, 1280, 1115, 926, 860, 760, and 733 cm^{-1}. PMR spectrum: 8.0 (d, 7-H), 8.35 (d, 2-H), and 9.8 ppm (broad s, NH).

8-Bromobenz[c,d]indolin-2-one-6-carboxylic Acid (VIII). A mixture of 1.7 g of acid VII, 20 ml of acetic acid, and 1.4 g of bromine was refluxed for 1 h, after which it was poured into 60 ml of water, and the precipitate was removed by filtration, washed, and dried to give 1.6 g of VIII with mp 350°C (from acetic acid). Found: C 49.1; H 2.6; Br 27.2; N 4.8%. $C_{12}H_6BrNO_3$. Calculated: C 49.3; H 2.1; Br 27.4; N 4.8%. IR spectrum: 1713, 1666, 1626, 1480, 1393, 1233, 1073, 900, 866, 815, 773, and 733 cm^{-1}. PMR spectrum: 7.83 (s, 5-H), 8.0 (d, 7-H), 8.35 (t, 2-H, 3-H), and 9.85 ppm (s, NH).

6-Bromo-N-acetylbenz[c,d]indolin-2-one (X). A mixture of 1.0 g of N-acetylbenz[c,d]indolin-2-one (IX), 15 ml of acetic acid, 5 ml of acetic anhydride, and 1.6 g of bromine was refluxed for 3 h, after which it was cooled and poured into water. The aqueous mixture was filtered, and the solid material was washed and dried to give 1.1 g of X with mp 162.5-163°C (from isopropyl alcohol). Found: Br 27.5%. $C_{13}H_8BrNO_2$. Calculated: Br 27.5%. IR spectrum: 1730, 1693, 1626, 1373, 1293, 1093, 976, 840, 760, and 733 cm^{-1}. PMR spectrum: 7.85 (m, 5-H), 8.00 (d, 7-H, 8-H), and 8.35 ppm (s, 2-H, 3-H, NH).

LITERATURE CITED

1. G. I. Bystritskii and S. V. Ovsyannikova, Zh. Org. Khim., 15, 2577 (1979).
2. G. I. Bystritskii, G. N. Vorozhtsov, N. S. Dokunikhin, and S. V. Ovsyannikova, Zh. Org. Khim., 11, 1731 (1975).
3. A. Stroll, T. Petrzilka, and J. Rutsman, Helv. Chim. Acta, 33, 2254 (1950).
4. R. N. Nurmukhametov, N. L. Belaits, and D. N. Shigorin, Zh. Fiz., Khim., 43, 869 (1969).
5. N. L. Belaits, R. N. Nurmukhametov, D. N. Shigorin, and G. I. Bystritskii, Zh. Fiz. Khim., 43, 1673 (1969).
6. G. N. Rodionova, L. N. Mova, G. N. Vorozhtsov, S. V. Ovsyannikova, and G. I. Bystritskii, Zh. Fiz. Khim., 55, 1760 (1981).

7. M. Dewar, Molecular Orbital Theory of Organic Chemistry, McGraw-Hill (1969).
8. G. N. Kagan, V. A. Kosobutskii, V. K. Belyakov, and O. G. Tarakanov, Khim. Geterotsikl. Soedin., No. 6, 794 (1972).
9. Yu. A. Kruglyak, G. G. Dyadyusha, V. A. Kuprievich, L. M. Podol'skaya, and G. N. Kagan, Methods for the Calculation of the Electronic Structures and Spectra of Molecules [in Russian], Naukova Dumka, Kiev (1969).

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

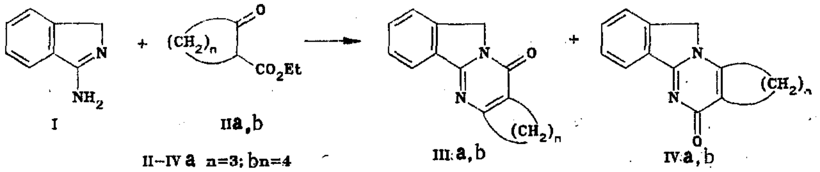
V. A. Kovtunenko, V. V. Ishchenko,
A. K. Tyltin, A. V. Turov,
and F. S. Babichev

UDC 547.759.4'859:543.
422.25:542.953.7

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.



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

---

T. G. Shevchenko Kiev State University, Kiev 252601. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1368-1371, October, 1985. Original article submitted September 10, 1984.

0009-3122/85/2110-1122$09.50