REACTION OF INDOLE-2-CARBOXYLIC ACID HYDRAZIDE WITH CARBONYL COMPOUNDS

N. A. Kogan and M. I. Vlasova

Only a few derivatives of indole-2-carboxylic acid hydrazide (I) have been described in the literature. Nevertheless, compounds which have carcinostatic [1], antinflammatory [2], and antituberculosis activity [3] are found among them. On the other hand, the reactions of aldehydes [4-6] and ketones [7, 8] with indole and its 1,2,3-substitutes have been studied in more detail. In the present work we investigated the reaction of aromatic aldehydes with compound I, which, as might be expected, should lead to the formation of new cyclic indole-containing systems, since the original molecule of compound I contains two reactive centers (positions 1 and 3) and the amino group of the hydrazide chain, which is four atoms away from them. A tendency toward cyclization in position 1 with the formation of 5-keto-4, 5-dihydroindoldiazine-(1:4) or in position 3 with the formation of 2-keto-1-methyl-2, 3-dihydro- γ -carboline was noted earlier in bis-(2-ethoxy)-ethylamidaindole-2-carboxylic acid [9]. In our experiments, compound I in reactions with benzaldehyde, aubepine, p-dimethylaminobenzaldehyde, piperonal, salicylaldehyde, vanillin, isovanillin, o-chlorobenzaldehyde, veratric aldehyde, and others produced normal reactions products: the 2-indoloylhydrazones of the corresponding aldehydes (Table 1), which are colorless crystalline compounds readily soluble in alcohol and dioxane. Their hydrochloride salts, which lose a molecule of acid when washed with water, can be recovered from absolute ethanol containing ether when dry hydrogen chloride is bubbled through. The hydrolysis of compound I and 1-methylindole-2-carboxylic acid hydrazide (II) in 0.1 N hydrochloric acid takes place very slowly even at a temperature of 50°C. A condensation reaction takes place with liquid aldehydes when the reagents are mixed at room temperature or when heated to 80° in an alcoholic medium. Aldehydes containing a phenolic hydroxyl (vanillin, isovanillin, and m-oxybenzaldehyde) reacted when the reagents were fused. The structure of the indoloylhydrozones which were obtained (IV-XV) did not evoke doubt. The absorption band of the carbonyl groups of compounds IV-XV lies in the region of 1640-1660 cm⁻¹, and a strong absorption band of C=N valence oscillations is found in the region of $1530-1540 \text{ cm}^{-1}$ and is absent from the original hydrazides. The UV spectra of compounds IV-XV, taken in alcoholic solution, have one maximum in the region of 330-350 nm, and in this case, as should be expected, electron-donor substitutes in the aldehyde part of the molecule

| Com- pound | Ar | Yield (in %) | Melting point (in de- grees) | N found (in %) | Empirical formula | N computed (in %) |
|---|--|--|--|--|--|--|
| IV VI VII VIII IX XI XII XIII XIV XV | $\begin{array}{c} C_{e}H_{5} \\ p^{-}CH_{3}OC_{6}H_{4} \\ m^{-}CH_{3}OC_{6}H_{4} \\ o^{-}ClC_{6}H_{4} \\ p^{-}HO^{-}m^{-}CH_{3}OC_{6}H_{3} \\ p^{-}(CH_{3})_{2}NC_{6}H_{4} \\ m^{-}HOC_{6}H_{4} \\ m^{-}HOC_{6}H_{4} \\ m^{-}NO_{2}C_{6}H_{4} \\ m^{-}NO_{2}C_{6}H_{4} \\ p^{-}(ClH_{2}CH_{2})_{2}NC_{6}H_{4} \\ 3,4^{-}[-O^{-}CH_{2}^{-}O^{-}]C_{6}H_{3} \end{array}$ | 95 90 92 94 94 92 93 92 93 92 96 96 92 91 | $\begin{array}{c} 184-5\\ 220-22\\ 180-81\\ 218-20\\ 198-9\\ 219-21\\ 286-8\\ 195\\ 289-90\\ 268-70\\ 130-3\\ 240\\ \end{array}$ | 16,04 14,28 14,31 14,12 13,68 18,42 14,95 15,08 18,12 18,03 13,60 13,53 | $\begin{array}{c} C_{16}H_{18}N_{3}O\\ C_{17}H_{18}N_{3}O_{2}\\ C_{17}H_{18}N_{3}O_{2}\\ C_{16}H_{12}CIN_{3}O\\ C_{17}H_{16}N_{3}O_{3}\\ C_{16}H_{12}CIN_{3}O\\ C_{17}H_{16}N_{3}O_{3}\\ C_{18}H_{18}N_{4}O\\ C_{16}H_{13}N_{3}O_{2}\\ C_{16}H_{13}N_{3}O_{2}\\ C_{16}H_{12}N_{4}O_{3}\\ C_{16}H_{12}N_{4}O_{3}\\ C_{16}H_{12}N_{4}O_{3}\\ C_{16}H_{12}N_{3}O_{3}\\ \end{array}$ | 15,96 14,33 14,33 14,14 13,59 18,30 15,05 15,05 15,05 18,18 18,18 13,8 13,68 |

| TABLE 1. 2- | Indolovlhydrazones | of | Aldehydes |
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cause a bathochromic shift. For some compounds (IV, VIII) a discontinuity in the curve is observed close to 280 nm which corresponds to the absorption of the indole chromophore.

The capacity of compound I to react with excess aldehyde in boiling amyl alcohol at a temperature above 130° with the production of compounds whose elementary composition indicated that two aldehyde residues are included in the newly formed molecule with the loss of two molecules of water was very unexpected. The hydrazide yield was 40-60%. The molecular weight of the compounds obtained was determined spectrophotometrically, based on the extinction of the indole chromophore, which in the compounds obtained was $1.6 \cdot 10^{-4}$ liter/mole. The extinction of the indole chromophore in I, in 3-methyl-indole-2-carboxylic acid hydrazide (III), and in II was first shown and was also $1.6 \cdot 10^{-4}$ liter/mole. Determination of the molecular weight by Rast's method produced a scatter of more than 30%, and in some cases could not be carried out at all in view of the fact that the compounds did not dissolve in a camphor melt.

The compounds obtained are colorless highly fusible crystalline substances which are poorly soluble in a majority of organic solvents and moderately soluble in dioxane and ethanol. On the basis of the chemical properties and UV and IR spectra, a 1,2-substituted 1,2-dihydropyrrolo(3,4-b)indolone-3 structure was proposed for these compounds. There are two reports in the literature about the finding of a heterocyclic system of 1, 2-dihydropyrrolo(2, 4-b)indole. This system was first obtained in the synthesis of indoles by Fisher's reaction from 2,3-dioxopyrrolidines [10], and recently by the same reaction from 3-ketopyrrolidine [11]. The compounds (XVI-XXII; Table 2) undergo slow acid hydrolysis with the splitting off of an aldehyde molecule. The reduction of XVI, XX, and XXI with Raney nickel in boiling dioxane causes rupture of the N-N bond with the splitting off of one aldehyde residue, which is indicated by the elementary analysis and the molecular weight of the products isolated. In this case, frequencies characteristic of the N-N (1450 cm⁻¹) and C=N (1540 cm⁻¹) bonds disappeared from the IR spectrum, and the maximum in the region of 330-350 nm, which reflects the absorption of the benzylidene part of the molecule, disappeared from the UV spectrum. In comparison with the unreduced compound, a bathochromic shift in the absorption maximum to 300 nm takes place (see Fig. 1), which confirms the proposed structure, since the absorption maximum of III is at 295 nm, and of the amide of indole-2-carboxylic acid is at 296 nm. The extinction of all three compounds is $1.6 \cdot 10^{-4}$ liter/mole.

The carbonyl frequencies of compounds XVI-XXII is $30-40 \text{ cm}^{-1}$ higher than that of the corresponding indoloylhydrazones IV-XV and are 1660-1680 cm⁻¹ as a result of the formation of a five-member cyclic system.

The increase in the carbonyl frequency of the N-methylated derivative of XVII to 1690 cm⁻¹ in comparison with XVI indicates the existence of a hydrogen bond between the imino group of the pyrrole ring and the carbonyl group of compounds XVI-XXII. The N-H valence oscillations of compounds XVI, XVIII-XXII are 3160-3200 cm⁻¹ and their absence from the spectrum of the N-methyl derivative of XVII confirms the correctness of the proposed structure of compounds XVI-XXII.

The mechanism of the production (see Scheme 1) of pyrrolo(3, 4-b)indolones-3, in our opinion, must involve the intramolecular reaction of the hydrated form of indoloylhydrazone (a) with the production of a cyclic six-member hydrazide, which, as is known [12], is rapidly regrouped into five-member cyclic N-aminoimides under the influence of temperature and excess aldehyde. This diagram is confirmed by the following experimental data. In absolute (anhydrous) amyl alcohol, the formation of pyrrolo(3, 4-b)indolones does not take place, whereas the addition of several drops of water leads to the desired reaction. It should be noted that the amide of indole-2-carboxylic acid does not enter into such reactions.

When position 3 of the indole ring is occupied, cyclization is accomplished through the imino group of the indole ring, which is indicated by the absence of absorption in the region of $2900-3600 \text{ cm}^{-1}$ from the IR spectrum of compound XXVIII.

We have found that the reaction does not stop with the formation of yyrrolo(3, 4-b) indolones-3. The presence in compounds XVI-XXII of mobile hydrogen atoms in position 1 leads to condensation of an aldehyde molecule with two molecules of yyrrolo(3, 4-b) indolone-3 with the production of the corresponding di[pyrrolo(3, 4-b) indolone-3-yl-1]-phenylmethanes (Table 3). (See Scheme on following page.)



The IR and UV spectra of the compounds obtained (XXIII-XXVI) differ little from those of the corresponding uncondensed products (XVI-XXII). The spectra contain the frequencies of NH groups, and during acid hydrolysis, compounds XXIII-XXVI split off the corresponding aldehyde, which excludes condensation on the hydrogen of the azomethyne group

Separation of compound XXIII from XVI is achieved by crystallization from acetic anhydride in which XVI is readily soluble.



Fig. 1. UV spectra of 1, 2-dihydropyrrolo(3, 4-b)indolones -3 in alcoholic solution, taken on an SF-4A instrument. Concentration $1.2 \cdot 10^{-4}$ g/liter.

The compounds obtained do not undergo acylation with boiling acetic anhydride, with the exception of those compounds which contain a phenolic hydroxyl on which attachment of the acetyl residue takes place. The action of various oxidizing agents at room temperature, hydrogen peroxide (10%) in a neutral medium, lead tetraacetate in glacial acetic acid, and potassium permanganate (3%) in acetic acid, did not cause changes in the compound.

It should be noted that when products containing chlorine and bromine (XX, XXI) were treated with pyrophoric nickel in boiling dioxane, reductive dehalogenation took place. Preliminary pharmacological tests showed that compounds XXI and XXII have a slight hypotensive effect.

EXPERIMENTAL

<u>Hydrazide of indole-2-carboxylic acid (I)</u>. 5.6 g of the ethyl ester of indole-2-carboxylic acid and 10 g of hydrazinehydrate are heated with stirring in a steam bath for 10 min,

| | | alógen | 3,21 |
|-------------------|---------------|-------------------|---|
| | in %) | H | 9,58533 9,58533 9,4888 9,58533 1000 11,500 11,960 1000 11,960 1000 1000 1000 1000 1000 1000 1000 1 |
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| | Con | c | 78,63 78,63 78,90 72,99 54,24 63,01 63,01 67,72 |
| | | Empirical iormuta | C32H17N5O C34H17N5O C34H17N5O C35H17N5O C35H13B12N5O C35H18B12N5O C35H18B12N5O C35H18L12N5O C35H12C12N5O C35H11N5O6 |
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| | ш | υ | 78,54 78,61 61,61 73,60 534,29 63,20 67,80 |
| 3,4-b)indolones-3 | Melting point | (in degrees) | 290 (from dioxane) 289—290 (from ethanol) 300—301 (from dioxane) 271—272 (from dioxane) 281—302 (from dioxane) 233, hardens, 273 (from ethanol) 259—260 (from ethanol) |
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| ŢABL | E 3. Di[pyrrolo(3, | , 4-b): | indolone-3-yl | -1]-ph | enylm | echanes | 70 | | | | | |
|-------|--|----------------------------|--|----------------------------------|---------------------------------------|-------------------------------|---------|---|----------------------------------|------------------------------|-------------------------------|---------|
| | | Viald | Melting moint | | Foùn | id (in %) | | | Cot | nputed | (in %) | |
| punod | Ar | (in %) | (in degrees) | c | Н | N | Halogen | Empirical formula | U | н | N | Halogen |
| | C ₄ H, m-CH ₃ -O-o-HOC ₆ H ₃ m-CH3) ₃ NC ₆ H ₄ o-ClC ₆ H ₄ | 34 58 68 86 89 | 289–290 259–260 294–295 260 (from alcohol) | 80,59 68,56 72,61 64,28 | 4,98 6,58 6,58 3,754 3,74 | 10,68 8,32 8,45 8,45 | 11,50 | C ₆₅ H ₄₈ N ₆ O ₂ C ₆₈ H ₄₈ N ₆ O ₂ C ₆₈ H ₄₈ N ₁₁ O ₂ 2H ₂ O C ₆₃ H ₅₃ CI ₅ N ₆ O ₂ | 80,50 68,13 63,69 63,69 | 4,81 6,43 3,70 3,70 | 10,63 8,23 8,41 8,41 | 17,77 |

cooled, and the crystalline precipitate of I filtered off. mp 245-246° (mp 241° according to the literature). Yield 4.6 g (88%). Hydrazides II and III are obtained by the method indicated above from the appropriate ethyl esters.

2-Indoloylhydrazone of benzaldehyde (IV). 1.7 g of I are mixed with 2.1 g of benzaldehyde for 10 min at $35-40^{\circ}$. The precipitate formed is ground in 15 ml of ethanol, filtered, and crystallized from ethanol. mp 184-185°. Yield 2.5 g (95%).

2-Indoloylhydrazones V, VII, and X are obtained by the method described above.

<u>2-Indoloylhydrazone of m-methoxybenzaldehyde (VI).</u> 1.7 g of I are heated with 2.6 g of m-methoxybenzaldehyde in 10 ml of amyl alcohol with stirring in a boiling water bath for 15 min. The precipitate which forms upon cooling is filtered off and crystallized from ethanol. Yield 2.7 g (92%). mp 180-181°.

2-Indoloylhydrazones VIII, IX, XI, XII, and XIII are obtained by the method indicated above.

 $\frac{1-(\text{Phenyl})-2-N-(\text{benzylidenamino})-1, 2-\text{dihydropyrrolo}(3, 4-b)-\text{indolone}-3 (XVI).}{\text{g of I and 3.2 g of benzaldehyde in 10 ml of amyl alcohol are mixed at the temperature of boiling alcohol until a precipitate forms in the reaction solution, which is immediately filtered off, washed with ethanol, and crystallized from dioxane. mp 290°. Mol. wt.: computed 351, found 353. Yield 1.9 g (54%).}$

Compounds XVII, XVIII, XIX, XX, and XXII are also obtained by method A.

<u>1-(o-Chlorophenyl)-2-N-(o-chlorobenzylidenamin) -1, 2-dihydropyrrolo(3, 4-b)indolone-3 (XXI).</u> Method B. A mixture of 1.5 g of VII and 2.1 g of o-chlorobenzaldehyde are mixed in 12 ml of water in a boiling water bath for 1 h. Four ml of ethanol are added to the cooled reaction mass. The precipitate which forms is filtered off and crystallized from ethanol. The product crystallizes with 1 mole of water. mp 253°, hardens at 273°. Yield 1.8 g (82%).

Di-[1-(phenyl)-2-N-(benzylidenamino)-1, 2-dihydropyrrolo(3, 4-b)-indolone-3-yl-1]-phenylmethane (XXIII). 1.7 g of I are mixed in 5.3 g of benzaldehyde at a temperature of 160° for 3 h. The precipitate which forms upon cooling is filtered off, washed with ethanol, and crystallized from dioxane. mp 289-290°. Mol. wt.: computed 790, found 770. Yield 1.6 g (36%).

Compounds XXIV-XXVI are obtained by method A.

<u>1-Phenyl-1, 2-dihydropyrrolo(3, 4-b)indolone-3 (XXVII)</u>. One g of XVI and 20 g of Raney nickel are heated with stirring in 200 ml of dioxane and 40 ml of water in a nitrogen current in a boiling water bath for 3 h. The hot reaction mass is rapidly filtered off. The solvent is distilled off in vacuo. The dry residue is crystallized from ethanol. mp 238°. Yield 0.58 g (75%). Found, %: C 77.48, H 4.90, N 11.08. $C_{16}H_{12}N_{20}$. Computed, %: C 77.41, H 4.83, N 11.29. Mol. wt.: computed 248, found 230 (by Rast's method).

Compounds XX and XXI are reduced in a similar way.

<u>1-N-(benzylidenamino)-2-phenyl-8-methyl-1, 2-dihydroimidazolo-(3, 4-a)indolone-9 (XXVIII).</u> 1.89 g of the hydrazide III and 2.12 g of benzaldehyde are heated with stirring in 10 ml of boiling amyl alcohol for 3 h. The residue of unreacted hydrazone which precipitates upon cooling is filtered off. The solvent is distilled off from the reaction solution in vacuo. The residue is ground in petroleum ether. The precipitate which forms is dissolved in ethyl ether. The ether solution is passed twice through a column containing aluminum oxide. The solvent is distilled off. The product is dried in vacuo. mp 74-76° (decomposes). Yield 2 g (55%). Found, %: C 79.11, H 5.28, N 11.40. $C_{24}H_{19}N_{3}O$. Computed, %: C 78.90, H 5.20, N 11.50.

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