

REACTION OF (OXINDOLYL)- AROYL CARBINOLS WITH 1,2-DIAMINES

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(Oxindolyl)arylcarbinols undergo condensation with 1,2-diamines to give 1,5-diazepine derivatives.

It has been shown [1] that (1-methyl-3-oxindolyl)arylcarbinols (I, $R = CH_3$) react with hydrazine hydrate in boiling alcohol to give 3'-arylspiro [(1-methyloxindole)-3,5'-(2-pyrazolines)], apparently through a step involving dehydration to the corresponding 3-phenacylidene derivative, the hydrazones of which subsequently undergo cyclization. It might have been assumed that carbinols I should react via an analogous scheme also with o-phenylenediamine, which reacts with α,β -unsaturated ketones to give 1,5-benzodiazepine (for example, see [2]). In fact, we found that a high-melting crystalline compound, for which we proposed the 1'-methyl-4-phenyl-2'-oxospiro(1H,3H-1,5-benzodiazepine-2,3'-indoline) structure (III, $R = CH_3$, $A = o$ -phenylene), is formed when carbinol I ($R = CH_3$) is refluxed with o-phenylenediamine in acetic acid.

The bands of the carbonyl and amide groups appear, respectively, at 1640 and 3250 cm^{-1} in the spectrum of a mineral oil suspension of the compound and at 1710-1730 (double peak) at 3420 cm^{-1} in the spectrum of a dichloroethane solution (0.6 mole/liter); this clearly confirms the intermolecular character of the hydrogen bond.

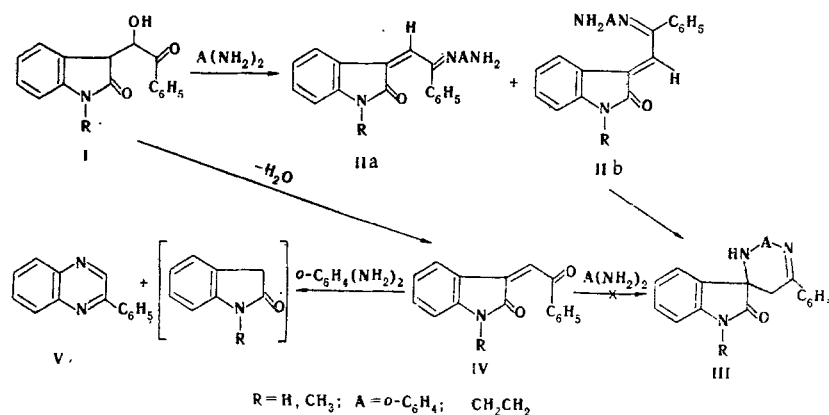
The PMR spectrum of III contains a singlet of two methylene protons in a seven-membered ring at 2.03 ppm and a singlet at 3.21 ppm (NCH_3); the singlet at 6.38 ppm possibly characterizes the proton of the NH group of the seven-membered ring. o-Phenylenediamine gives 1,5-diazepine of the III type also with (3-oxindolyl)benzoylcarbinol and (1-methyl-3-oxindolyl)(p-toluy)carbinol. Partial simultaneous splitting out of an oxindole residue to give the corresponding quinoxaline derivative (V) is also noted in all cases. 1,5-Diazepines III do not form hydrochlorides.

Carbinols I react similarly with ethylenediamine. In the case of (1-methyl-3-oxindolyl)benzoylcarbinol we were able to make a more detailed investigation of the dependence of the course of the reaction on the conditions used. For example, it was found that in refluxing alcohol after 30 min the reaction stops at the step involving the formation of an imine of the II type, whereas, in addition to imine II (isolated in 30% yield), light-yellow crystals of the 1,4-diazepine derivative (III, $R = CH_3$, $A = CH_2CH_2$) can also be isolated when the mixture is refluxed for a long time (on the order of 25 h). The yield of the 1,4-diazepine derivative can be raised to 32% when the starting compounds are refluxed in ethylenediamine for 5 h.

It is essential to note that imine II is not converted to the expected 1,4-diazepine derivative on prolonged refluxing. We therefore suppose that the reaction evidently gives two compounds of this type - imines IIa and IIb which differ with respect to the geometrical configuration of the $C = C$ bond, of which one was converted to a 1,4-diazepine, and the other, the configuration of which does not favor this sort of transformation for steric reasons, was isolated as one of the reaction products.

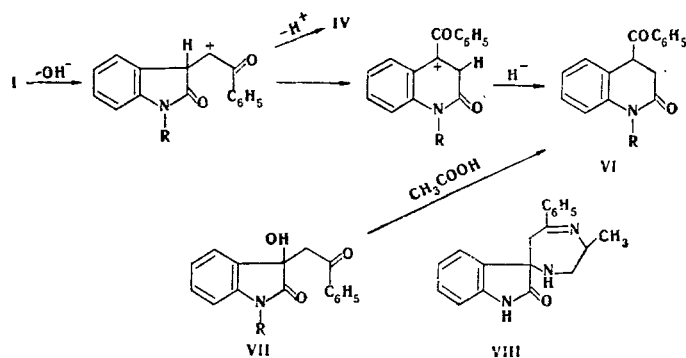
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A mixture of three products that are separable by chromatography with a column filled with silica gel is formed in refluxing acetic acid. The mixture contains the dehydration product, 1-methyl-3-phenacylidene-oxindole (IV, $R = CH_3$), an imine (II, $R = CH_3$, $A = CH_2CH_2$), and a colorless compound of unknown structure. The latter is evidently the product of conversion of the starting carbinol under the influence of the acidic agent, because it is formed on prolonged refluxing of the starting carbinol itself in acetic acid. Intense carbonyl absorption appears in its IR spectrum at 1710 and 1685 cm^{-1} . The mass spectrum contains a molecular ion peak at 265* and fragment ion peaks at 160 (100%) and 132 (28%), which is due to subsequent detachment of carbon monoxide, and at 117 (41%) and 105 (C_6H_5CO) (71%). It might be assumed that the starting carbinol loses a hydroxyl group under the influence of acid (acetic acid in this case) to give a cation, which is subsequently partially converted to dehydration product IV; IV undergoes partial Wagner-Meerwein rearrangement to quinoline derivative VI, which we also isolated along with two other compounds. It is interesting that the same substance is formed by prolonged refluxing of 1-methyl-3-phenacyldioxindole (VII) in acetic acid in the presence of ethylenediamine in 30% yield (apparently as a result of a double Wagner-Meerwein rearrangement).

In the case of the reaction of carbinols I with o-phenylenediamine we were unable to establish the presence of this quinoline derivative.



(3-Oxindolyl)benzoylcarbinol (I, $R = H$) in refluxing ethylenediamine gives the expected diazepine III ($R = H$, $A = CH_2CH_2$), whereas in refluxing 1,2-diaminopropane under these conditions we observed the formation of a compound for which we propose the 2-methyl-7-phenyl-2'-oxospiro[1(7)-dehydro-1,4-diazacycloheptane-5,3'-indoline] structure (VIII).

EXPERIMENTAL

The individuality of all of the compounds obtained in this study was confirmed by chromatography on Silufol UV-254 plates. The plates were developed in UV light or with iodine vapors. The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord-71-IR spectrometer. The UV spectra of methanol solutions were recorded with a Specord UV-vis spectrophotometer. The PMR spectrum of a deuterio-pyridine solution was obtained with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. The melting points were determined with a Boetius apparatus.

Condensation of (1-Methyl-3-oxindolyl)benzoylcarbinol with o-Phenylenediamine. A solution of 1.45 g (0.005 mole) of the carbinol and 0.54 g (0.005 mole) of o-phenylenediamine in 10 ml of acetic acid was refluxed

* Here and subsequently, the m/e values are presented for the corresponding ions.

for 90 min, after which it was cooled and poured into 100 ml of water. The aqueous mixture was made alkaline and extracted with benzene. The extract was washed with water and dried with sodium sulfate, and the solvent was removed completely by distillation. The residue was passed through a column filled with aluminum oxide with elution by benzene-petroleum ether (1:1) to give 0.51 g of colorless needles of 2-phenylquinoxaline with mp 77° (from petroleum ether; mp 78° [3]). IR spectrum: ν_{\max} 1620, 1550, 1380, 1315, and 1210 cm^{-1} . Elution with benzene-petroleum ether (2:1) gave 1.2 g (68%) of yellow crystals of 1'-methyl-4-phenyl-2'-oxo-spiro(1H,3H-1,5-benzodiazepine-2,3'-indoline). IR spectrum: ν_{\max} 3330, 1635, 1620, 1590, 1380, 1370, 1310, and 1265 cm^{-1} . Found: C 77.8; H 5.6; N 11.7%. $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}$. Calculated: C 78.2; H 5.4; N 11.9%.

Condensation of (1-Methyl-3-oxindolyl)(p-toluy)carbinol with o-Phenylenediamine. Workup of the reaction mixture obtained from 2.95 g (0.01 mole) of the carbinol and 1.08 g (0.01 mole) of o-phenylenediamine gave 0.8 g (38%) of colorless needles of 2-(p-tolyl)quinoxaline with mp 95° (from petroleum ether). Found: C 81.8; H 5.5; N 13.0%. $\text{C}_{15}\text{H}_{12}\text{N}_2$. Calculated: C 81.8; H 5.4; N 12.7%. IR spectrum: ν_{\max} 1610, 1580, 1550, 1380, 1315, and 1210 cm^{-1} . Also obtained was 1.8 g (50%) of yellow crystals of 1'-methyl-4-(p-tolyl)-2'-oxo-spiro(1H,3H-1,5-benzodiazepine-2,3'-indoline) with mp 130° (from methanol). IR spectrum: ν_{\max} 3250, 1640, 1620, 1590, 1510, and 1360 cm^{-1} . Found: C 78.3; H 5.7; N 11.2%. $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}$. Calculated: C 78.2; H 5.7; N 11.4%.

Condensation of (3-Oxindolyl)benzoylcarbinol with o-Phenylenediamine. A solution of 13.5 g (0.05 mole) of the carbinol and 5.4 g (0.05 mole) of o-phenylenediamine in 50 ml of acetic acid was refluxed for 2 h, after which it was cooled and poured over ice. The aqueous mixture was neutralized with aqueous alkali, and the resulting precipitate was separated and crystallized from methanol to give 6.1 g of 4-phenyl-2'-oxospiro(1H,3H-1,5-benzodiazepine-2,3'-indoline) as white plates with mp 255°. IR spectrum: ν_{\max} 3295, 1660, 1610, 1590, and 1530 cm^{-1} . Found: C 78.6; H 5.5; N 12.2%. $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}$. Calculated: C 77.9; H 5.0; N 12.4%.

The filtrate was passed through a column filled with silica gel. Elution with benzene gave 2.88 g of 2-phenylquinoxaline followed by 0.7 g of 1,5-benzodiazepine.

Condensation of (1-Methyl-3-oxindolyl)benzoylcarbinol with Ethylenediamine. A) A mixture of 1.2 g (0.0036 mole) of the carbinol, 0.4 g (0.051 mole) of ethylenediamine, and 15 ml of alcohol was refluxed for 30 min, after which it was allowed to stand at room temperature overnight. The alcohol was evaporated to half the original volume, and the precipitated red crystals of imine II were removed by filtration to give 0.6 g (54%) of a product with mp 190-191° (from alcohol). IR spectrum: ν_{\max} 1100, 1245, 1260, 1560, 1610, and 1650 cm^{-1} . Found: C 74.5; H 5.9; N 13.7%. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$. Calculated: C 74.5; H 6.2; N 13.7%.

B) A mixture of 1.2 g of the carbinol, 0.4 g of ethylenediamine, and 15 ml of alcohol was refluxed for 25 h, after which the alcohol was removed by distillation, and the residual mixture was separated by chromatography with a column filled with silica gel to give 0.4 g (36%) of the above-described imine II and 0.1 g (9%) of light-yellow crystals of 1'-methyl-7-phenyl-2'-oxospiro[1(7)-dehydro-1,4-diazacycloheptane-5,3'-indoline] (III, R = CH₃, A = CH₂CH₂) with mp 219-220° (from aqueous methanol). IR spectrum: ν_{\max} 3250, 1630, 1595, 1490, 1460, 1380, and 1270 cm^{-1} . UV spectrum, λ_{\max} (log ϵ): 211 (4.42), 270 (4.15), 273 (4.18), 281 (4.23), and 345 nm (4.22). Found: C 73.0; H 6.0; N 12.8%. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O} \cdot 1/2\text{H}_2\text{O}$. Calculated: C 72.6; H 6.0; N 13.3%.

C) A 1.2-g (0.0036 mole) sample of the carbinol was refluxed with 12 ml of ethylenediamine for 5 h, after which the mixture was cooled and the resulting precipitate was removed by filtration. Alcohol (1.5 ml) was added to the filtrate, and the additional small amount of precipitate was removed by filtration. The combined precipitates were recrystallized twice from acetone and once from methanol to give 0.35 g (32%) of a product with mp 219-220°. With respect to its chromatographic behavior and spectral characteristics, the product was identical to diazepine III obtained in the preceding experiment. No melting-point depression was observed for a mixture of this product with a genuine sample.

D) A 0.6-ml sample of ethylenediamine was added dropwise to a solution of 0.9 g (0.0027 mole) of the carbinol in 10 ml of glacial acetic acid, and the mixture was stirred and refluxed for 4 h. It was then cooled, neutralized with dilute sodium carbonate solution, and extracted with chloroform. The extract was dried with sodium sulfate, the solvent was evaporated completely, and the residue was separated by chromatography with a column filled with silica gel. Chloroform eluted the following compounds successively: 1) 0.05 g of 1-methyl-3-phenacylideneoxindole with mp 122-123° (from methanol); 2) 0.082 g of red crystals of imine II with mp 190-191°; 3) 0.24 g of white crystals of 1-methyl-2-keto-4-benzoyl-1,2,3,4-tetrahydroquinoline (IV) with mp 135-136° (from methanol). IR spectrum: ν_{\max} 765, 1090, 1130, 1220, 1360, 1380, 1470, 1685, and 1710 cm^{-1} . Found: C 76.9; H 5.7; N 5.2%. $\text{C}_{17}\text{H}_{15}\text{NO}_2$. Calculated: C 77.0; H 5.7; N 5.3%.

To ascertain the origin of quinolone VI, 0.5 g of the carbinol was refluxed for 4 h in 15 ml of acetic acid. The mixture was then worked up as described above, and the product was separated by chromatography with a column filled with silica gel to give 0.2 g of 1-methyl-3-phenacylideneoxindole (IV, R = CH₃) and 0.01 g of quinolone VI (R = CH₃). No melting-point depression was observed for a mixture of this product with the quinolone obtained in the preceding experiment, and the samples had identical R_f values [in a chloroform-methanol (10:1) system].

1-Methyl-4-benzoyl-1,2,3,4-tetrahydro-2-quinolone from 1-Methyl-3-phenacyldioxindole. A mixture of 1 g of 1-methyl-3-phenacyldioxindole, 1 ml of ethylenediamine, and 10 ml of acetic acid was refluxed for 4 h, after which it was cooled, diluted with water, neutralized with sodium bicarbonate, and extracted with chloroform. Workup of the extract gave 0.3 g (30%) of a substance that was identical to quinolone VI obtained above with respect to its melting point and chromatographic behavior.

Condensation of (3-Oxindolyl)benzoylcarbinol with Ethylenediamine. A mixture of 4 g (0.015 mole) of the carbinol and 40 ml of ethylenediamine was refluxed for 4 h, after which it was cooled and poured into water. The product was extracted with chloroform, and the extract was washed with water, dried with sodium sulfate, and evaporated completely. The residue was crystallized successively from acetone and methanol to give 2.2 g (51%) of 7-phenyl-2'-oxospiro[1(7)-dehydro-1,4-diazacycloheptane-5,3'-indoline] with mp 221-222°. IR spectrum: ν_{\max} 3280, 1640, 1590, 1490, 1310, and 1230 cm⁻¹. UV spectrum, λ_{\max} (log ϵ): 209 (4.47), 272 (4.11), 278 (4.21), and 349 nm (4.22).

2-Methyl-7-phenyl-2'-oxospiro[1(7)-dehydro-1,4-diazacycloheptane-3,5'-indoline] (VIII). A solution of 2 g of the carbinol in 6 ml of propane-1,2-diamine was refluxed for 3 h, after which it was allowed to stand overnight. The resulting precipitate was removed by filtration, the filtrate was diluted with water, and the additional small amount of precipitate was removed by filtration. The precipitates were combined and washed with ether, and the residual solid was recrystallized from aqueous methanol to give 1.3 g (56%) of VIII with mp 220-222°. IR spectrum: ν_{\max} 1640, 1590, 1490, 1450, 1380, 1320, and 1300 cm⁻¹. Found: C 72.4; H 6.5; N 13.8%. C₁₉H₁₉N₃O · 1/2 H₂O. Calculated: C 72.6; H 6.4; N 13.4%.

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