SYNTHESIS OF INDOLES CONDENSED WITH A BICYCLO[3.3.1]NONANE SKELETON

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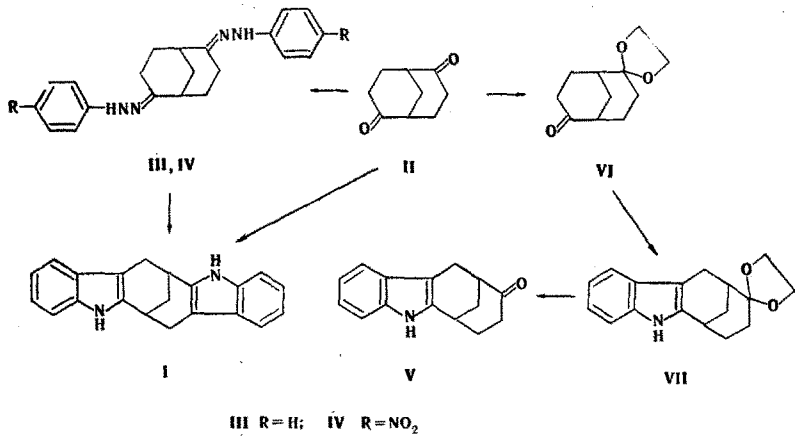
Derivatives of mono- and bisindoles condensed with a bicyclo[3.3.1]nonane skeleton were synthesized from bicyclo[3.3.1]nonane-2,6-dione and 6-hydroxybicyclo[3.3.1]nonan-2-one by means of the Fischer reaction.

The Fischer cyclization of phenylhydrazones is the most widely used method in the synthesis of indoles. This reaction has heretofore been studied from both synthetic [1, 2] and theoretical [3, 4] points of view. Despite the fact that the amount of literature with respect to this problem is enormous, many synthetic aspects remain to be studied. In particular, rather little is known regarding the behavior of bicyclic and carcass structures in the Fischer synthesis of indoles, although carbonyl derivatives of this type are well known, and the combination in one structure of the fragments of indole, the derivatives of which have a large complex of pharmacological properties, and a carcass or bicyclic structure may lead to the appearance of interesting features.

In the present research we studied the synthesis of indole structures that contain a bicyclo[3.3.1]nonane fragment, particularly diindolo[2, 3-b; 2, 3-f]-bicyclo[3.3.1]nona-2,6-diene (I). Due to the fact that the bicyclo[3.3.1]nonadiene fragment in this compound is chiral (C_2 symmetry), this compound will be chiral, and indole will be the only chromophore in this structure. So far as we know, this would be the first example of a compound with molecular asymmetry in a compound with an indole chromophore.

The starting compound for the synthesis was diketone II, which is readily obtained from the so-called "Meerwein ester" [5]. Bis(phenylhydrazone) III was obtained by treatment of diketone II with a solution of phenylhydrazine in 50% acetic acid at room temperature. Bis(p-nitrophenylhydrazone) IV was obtained by refluxing diketone II with p-nitrophenylhydrazine in the presence of 85% phosphoric acid. Bis(phenylhydrazone) III can be converted by means of the Fischer reaction under the influence of



a mixture of phosphoric acid and phosphoric anhydride to diindolo derivative I, which also can be obtained by the addition of an alcohol solution of diketone II to a refluxing aqueous alcohol solution of phenylhydrazine.

Treatment of an alcohol solution of monoethylene ketal VI (obtained by the method in [6]) with a solution

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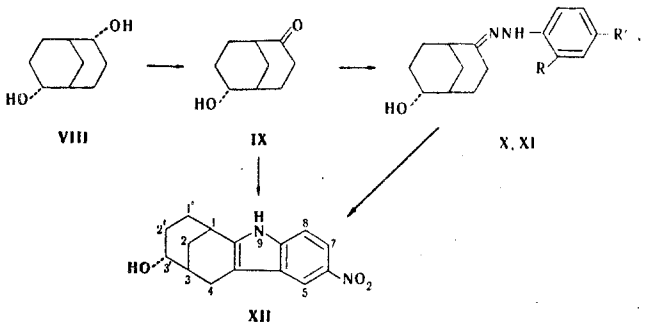
of phenylhydrazine in acetic acid leads to ethylene ketal VII, which gives indolo[2,3-b]bicyclo[3.3.1]non-2-en-6-one (V) when it is heated in 2 N sulfuric acid.



VIII IX X, XI

XII

X R = H, R' = NO_2; XI R = NO_2, R' = H

A mixture of compounds II, VIII, and IX, from which pure endo-6-hydroxybicyclo[3.3.1]nonan-2-one (IX) was isolated by chromatography, was obtained by oxidation of diol VIII with the Jones reagent.

A mixture, from which we were able to isolate two principal reaction products – hydrazone X and indole derivative XII – by chromatography, is formed in an attempt to obtain the p-nitrophenylhydrazone (X) of the endo ketol in sulfuric acid. When the reaction is carried out in phosphoric acid at room temperature, the composition of the reaction products does not change. Brief refluxing (30 min) of the reaction mixture leads to a single reaction product – nitroindole XII. The yield of XII decreases when the refluxing period is extended, and a complex mixture of reaction products is formed. Nitroindole XII can also be obtained by cyclization of p-nitrophenylhydrazone X in the presence of polyphosphoric acid esters.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were obtained with a Spectromom 202 spectrophotometer. The PMR spectra of the compounds were obtained with a Tesla BS 487C spectrometer with hexamethyldisiloxane as the internal standard.

Bicyclo[3.3.1]nona-2,6-dione Bis(phenylhydrazone) (III). A solution of 0.9 g (82 mmole) of phenylhydrazine in 20 ml of 50% acetic acid was added to a solution of 0.6 g (4.2 mmole) of dione II in 16 ml of ethanol, and the precipitate was removed by filtration and washed with water and alcohol to give 1.2 g (92%) of bis(phenylhydrazone) III with mp 214-215 deg C (from aqueous alcohol). IR spectrum: 1610 cm^{-1} (C=N); no C=O absorption is present. Found: C 75.5; H 7.2; N 16.6%. $C_{21}H_{24}N_4$. Calculated: C 75.9; H 7.3; N 16.8%.

Bicyclo[3.3.1]nonane-2,6-dione Bis(p-nitrophenylhydrazone) (IV). A 13.5-ml sample of a solution of p-nitrophenylhydrazine (1.4 mmole), obtained from 0.78 g of p-nitrophenylhydrazine, 25 ml of 85% phosphoric acid, and was added to a solution of 0.1 g (0.7 mmole) of diketone II in 2.5 ml of alcohol, 25 ml of alcohol, and the mixture was refluxed for 30 min. It was then cooled and treated with 5 ml of water, and the precipitate was removed by filtration to give 1.1 g (84%) of bis(p-nitrophenylhydrazone) IV with mp 240-245 deg C (from aqueous alcohol). IR spectrum: 1610 cm^{-1} (C=N); no C=O absorption is present. Found: N 19.8%. $C_{21}H_{22}N_6O_4$. Calculated: N 19.9%.

Diindolo[2,3-b; 2,3-f]bicyclo[3.3.1]nona-2,6-diene (I). A) A solution of 0.76 g (5.3 mmole) of diketone II in 15 ml of alcohol was added with stirring to a refluxing mixture of 10 ml of alcohol, 3 ml of water, 1 ml of concentrated hydrochloric acid, and 1.98 g (18.3 mmole) of phenylhydrazine, and the mixture was refluxed for another 20 min. It was then cooled, and the precipitate was removed by filtration and washed with water and alcohol to give 1.37 g (65%) of diindole I with mp > 300 deg C (from acetone). UV spectrum, λ_{max}(log ε): 232 (4.75) and 485 nm (4.13). Found: C 84.5; H 6.1; N 9.5%. $C_{21}H_{18}N_2$. Calculated: C 84.5; H 6.1; N 9.4%.

B) A 1.2-g (3.7 mmole) sample of bis(phenylhydrazone) III was added with stirring to a mixture of 6 g (60 mmole) of phosphoric acid and 0.5 g of phosphoric anhydride, during which the temperature of the mixture rose rapidly. The mixture was then cooled, and a small amount of water was added cautiously. The resulting precipitate was removed by filtration and washed with water to give 1.03 g (96%) of diindole I, which was identical to the compound described above.

Indolo[2,3-b]bicyclo[3.3.1]non-2-en-6-one Ethyleneketal (VII). Acetic acid (20 ml) and 12 g (110 mmole) of phenylhydrazine were added to a solution of 9.8 g (53 mmole) of monoethyleneketal VI [6] in 50 ml of alcohol, and the mixture was heated at 80 deg C for 1 h. It was then cooled, and the resulting crystals were removed by

filtration and washed with water and a small amount of alcohol to give 7.4 g (55%) of ketal VII with mp 185-187 deg C (from absolute alcohol). IR spectrum: 3410 cm^{-1} (N—H); no C=O absorption band is present. UV spectrum, λ_{max}(log ε): 229 (4.54) and 283 nm (3.84). Found: N 4.8%. $C_{17}H_{19}NO_2$. Calculated: N 5.2%.

Indolo[2, 3-b]bicyclo[3.3.1]non-2-en-6-one (V). A mixture of 2 g (7.4 mmole) of VII and 24 ml of 2 N sulfuric acid was stirred at 50-60 deg C for 24 h, after which it was cooled and filtered to give 1.58 g (94%) of indole V with mp 151-153 deg C (from alcohol). IR spectrum: 3400 (N—H) and 1705 cm^{-1} (C=O). UV spectrum, λ_{max}(log ε): 224 (4.66) and 283 nm (4.03). Found: C 79.5; H 6.7; N 6.0%. $C_{15}H_{15}NO$. Calculated: C 80.0; H 6.7; N 6.2%.

endo-6-Hydroxybicyclo[3.3.1]nonan-2-one (IX). A 25-ml sample of the Jones reagent (1 g of chromic anhydride, 0.8 ml of concentrated sulfuric acid, and 75 ml of water) was added dropwise with vigorous stirring at room temperature to a solution of 1.55 g (0.6 mmole) of diol VIII [7] in 250 ml of acetone, and the mixture was evaporated to dryness. The residue was dissolved in the minimum amount of chloroform, and the solution was chromatographed with a column (with a length of 65 cm and a diameter of 2 cm) filled with aluminum oxide. The fraction containing ketol IX [R_f 0.54, chloroform—methanol (29 : 1)] was collected and dried with magnesium sulfate, and the solvent was removed by distillation to give 0.7 g of ketol IX with mp 172-174 deg C (after two sublimations). IR spectrum (CCl_4): 3635 (OH) and 1725 cm^{-1} (C=O). PMR spectrum ($CHCl_3$): 1.37-2.5 (m, 12 H), 2.51 (s, 1H), and 3.81 ppm (m, 1H, the width at half the height of the peak is ≈14 Hz). Found: C 70.4; H 8.9%. $C_9H_{14}O_2$. Calculated: C 70.1; H 9.1%.

6-Nitro-1,3-(3'-hydroxypropano)-1,2,3,4-tetrahydrocarbazole (XII). A) A 6.7-ml (0.7 mmole) sample of a solution of p-nitrophenylhydrazine (0.39 g of p-nitrophenylhydrazine was dissolved in 12 ml of 85% of phosphoric acid and 12.5 ml of alcohol) was added to a solution of 0.1 g (0.7 mmole) of endo-ketol IX in 2.5 ml of ethanol, and the mixture was refluxed for 30 min. It was then cooled, and water was added until a precipitate appeared. The precipitate was removed by filtration to give 0.09 g (53%) of indole derivative XII with mp 249-252 deg C (from aqueous alcohol). PMR spectrum (CF_3COOH): 1.25-2.6 (m, 11H), 3.80 (m, 1H), 4.88 (m, 1H), and aromatic protons at 6.85 (d, 1H, $J_{8,7}$ = 9 Hz), 7.51 (dd, 1H, $J_{7,8}$ = 9 Hz, $J_{7,5}$ = 2 Hz), and 7.94 ppm (s, 1H). Found: C 66.8; H 6.6; N 10.0%. $C_{15}H_{16}N_2O_3$. Calculated: C 66.2; H 5.9; N 10.3%.

B) A 50-ml sample of a solution of p-nitrophenylhydrazine (6.5 mmole) (1.2 g of p-nitrophenylhydrazine, 9 ml of concentrated sulfuric acid, 6 ml of water, and 45 ml of methanol) was added to a solution of 0.5 g (3.5 mmole) of ketol IX in 10 ml of methanol, and the mixture was allowed to stand at room temperature for 12 h. Water was then added until a precipitate appeared, half the volume of the solvent was removed by distillation, and the precipitate was removed by filtration and chromatographed with a column filled with aluminum oxide (elution with chloroform) to give 0.2 g of a yellow substance (R_f 0.21 and mp 250-252 deg C), which was identical to indole derivative XII, and 0.15 g of p-nitrophenylhydrazone X with mp 158-160 deg C [R_f 0.13, chloroform—methanol (29 : 1)]. IR spectrum: broad band at 3350 cm^{-1}; no C=O absorption is present. Found: C 62.2; H 6.7; N 14.4%. $C_{15}H_{19}N_3O_3$. Calculated: C 62.3; H 6.6; N 14.5%.

C) Polyphosphoric acid esters (0.075 g) [8] were added to a solution of 0.015 g of p-nitrophenylhydrazone X in the minimum amount of chloroform, and the mixture was refluxed for 30 min. Half the volume of solvent was removed by distillation, the concentrate was cooled, and the precipitate was removed by filtration to give 0.01 g of indole derivative XII, which was identical to the compound described above.

endo-Bicyclo[3.3.1]nonan-6-ol 2-(o-Nitrophenyl)hydrazone (XI). A 6.7-ml sample (0.7 mmole) of a solution of o-nitrophenylhydrazine (0.39 g of o-nitrophenylhydrazine was dissolved by heating in 12.5 ml of 85% phosphoric acid, the solution was cooled, and 12.5 ml of alcohol was added) was added to a solution of 0.1 g (0.7 mmole) of endo-ketol IX in 2.5 ml of alcohol, and the mixture was refluxed for 30 min. It was then cooled to room temperature, and water was added until a precipitate appeared. The precipitate was isolated by centrifugation to give 0.07 g of hydrazone XI with mp 93-96 deg C (from aqueous alcohol). PMR spectrum (C_5D_5N): 1.4-2.5 (m, 12 H), 2.61 (s, 1H), 3.90 (m, 1H), 6.55-8.1 (m, 4H), and 10.58 ppm (s, 1H). Found: C 62.0; H 6.4%. $C_{15}H_{19}N_3O_3$. Calculated: C 62.3; H 6.6%.

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REACTION OF FUNCTIONALLY SUBSTITUTED VINYL ETHERS WITH 3,4-DIAMINOFURAZAN AND FURAZAN-3,4-DICARBOXYLIC ACID DIHYDRAZIDE

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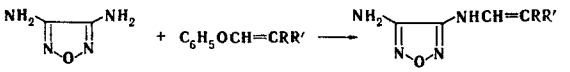
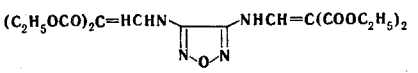
Enaminofurazans were obtained by reaction of vinyl ethers with 3,4-diaminofurazan. It was established by IR and PMR spectroscopy that enaminofurazans exist in the form of a chelate complex. The structure of the chelate complex is discussed. Enehydrazides were obtained by reaction with furazan-3,4-dicarboxylic acid dihydrazide. When there is a cyano group in the ether molecule, the reaction does not stop with the formation of the enehydrazide but continues with its cyclization to give a pyrazole ring.

Diverse condensed systems are obtained by the reaction of functionally substituted vinyl ethers with aromatic and heterocyclic amines. We have investigated the reactions of 3,4-diaminofurazan (I) and furazan-3,4-dicarboxylic acid dihydrazide (II) with vinyl ethers containing keto, ester, and cyano groups.

The corresponding enamines III-IX were obtained in all cases in the reactions of the vinyl ethers with furazan I. Dienamine X was obtained when the reaction was carried out with excess ethoxymethylenemalonic ester. An analysis of the PMR spectra shows that the enamines obtained exist in the form of a chelate cyclic

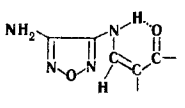


I III-IX



X

complex with a hydrogen bond between the proton of the amino group and the oxygen atom of the C=O group (XI). The formation of a hydrogen bond leads to slow exchange of the NH proton, as a result of which spin–spin coupling of the NH and CH protons with a constant of 13 Hz shows up in the PMR spectra. Such a large constant is characteristic for coupling of the NH and CH protons in the anti orientation that is realized in the chelate-bonded cis-s-cis form [1]. The presence of this form is also confirmed by the characteristic marked shift of the signal of the NH proton to weak field (10-12 ppm) [1].



XI

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