INDOLE DERIVATIVES

XXV*. The Structure of the Fischer Cyclization Products of Arylhydrazones of 4-Thiepanone and Its S, S-Dioxide

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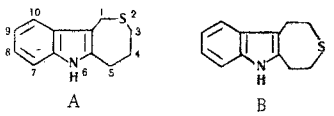
The Fischer cyclization of arylhydrazones of 4-thiepanone leads to 1, 3, 6H, 4, 5-dihydrothiepino[4, 3-c]indoles, while the cyclization of arylhydrazones of the S, S-dioxide of 4-thiepanone forms 6H-1, 2, 4, 5-tetrahydrothiepino[5, 4-c]indole.

In the Fischer cyclization of arylhydrazones of the unsymmetrical 4-thiepanone one might expect the formation of two series of isomers. Type A, with the 1, 3, 6H-4, 5-dihydrothiepino[4, 3-c]indole system, and type B, with the 6H-1, 2, 4, 5-tetrahydrothiepino[5, 4-c]indole system.



A B

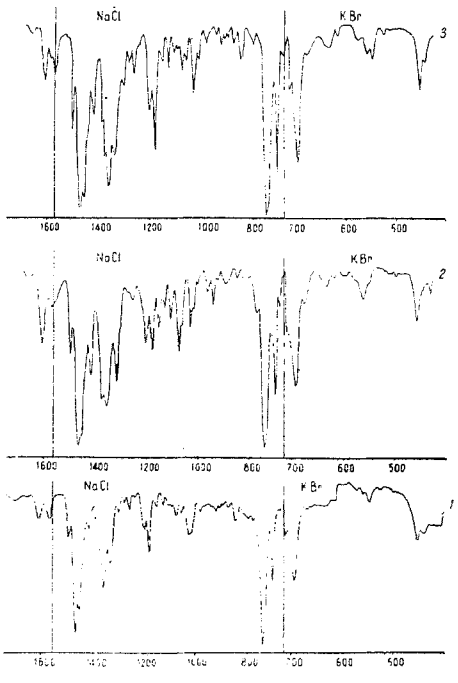


Fig. 1. IR spectra: 1) 1-benzyl-3-methyl-2-propylindole (IV); 2) 1-benzyl-3-methyl-2-propylindole (II); 3) 1-benzyl-2, 3-diethylindole (III).

As has been shown previously [2], in all cases of Fischer cyclization we were able to isolate only one isomer. We assumed that the latter was of type B on the basis of the reductive desulfonation of substance I—the product of the condensation of 4-thiepanone with N-benzyl-N-phenylhydrazine and of a comparison of the UV and IR spectra and chromatographic behavior of the indole II so obtained with the possible desulfonation product 1-benzyl-2, 3-diethylindole (III).

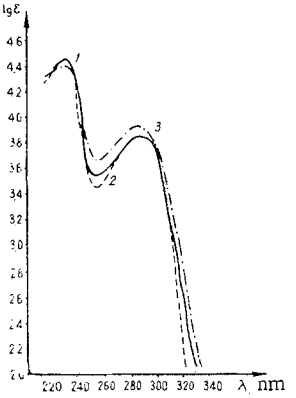


Fig. 2. UV spectra: 1) 1-benzyl-3-methyl-2-propylindole (IV); 2) 1-benzyl-2, 3-diethylindole (III); 3) 1-benzyl-3-methyl-2-propylindole (II).

In the present work we have synthesized 1-benzyl-3-methyl-2-propylindole (IV)—a possible product of the desulfonation of a thiepinoindole of type A. For this purpose, 2-propylindole [3] was converted by the Vilsmeier reaction into 3-formyl-2-propylindole (V), and the latter was reduced with lithium aluminum hydride to 3-methyl-2-propylindole (VI), the benzylation of which gave the indole IV. On chromatography in a thin layer of alumina (activities II and IV), substances 3 and 4, and also the indole II, had similar R_f values. The UV and IR spectra of these three substances also proved to be similar (Figs. 1 and 2), which showed that the conclusion to which we had come previously concerning the structure of the thiepinoindoles could be erroneous.

*For communication XXIV, see [1].

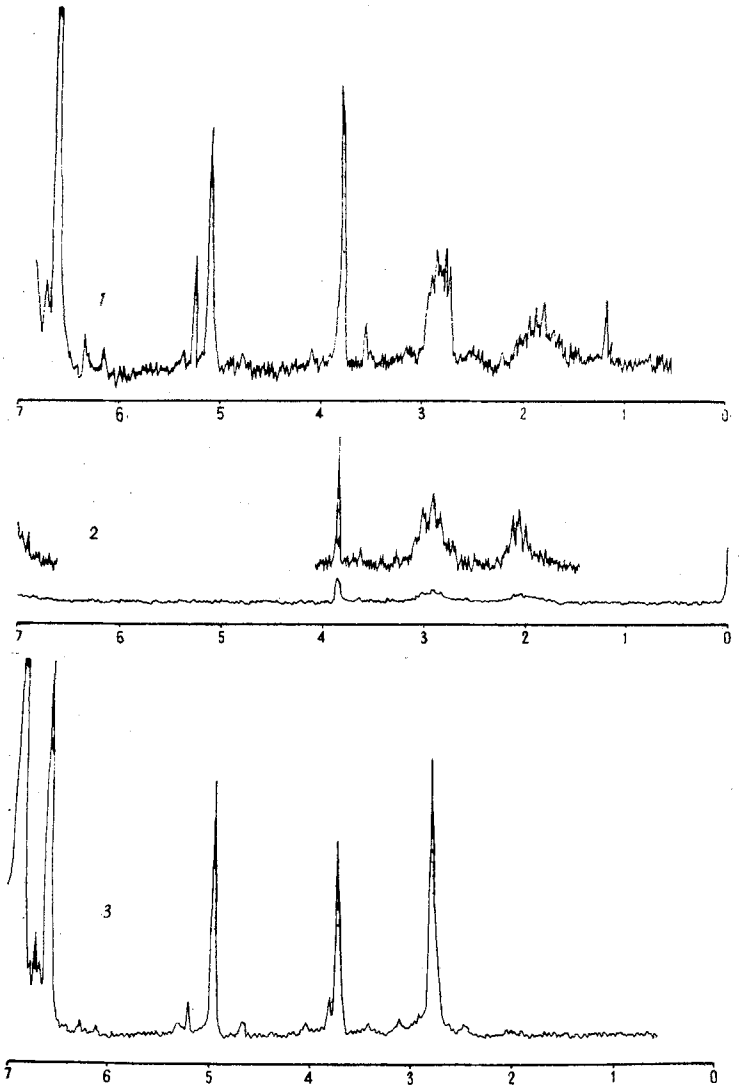


Fig. 3. PMR spectra.

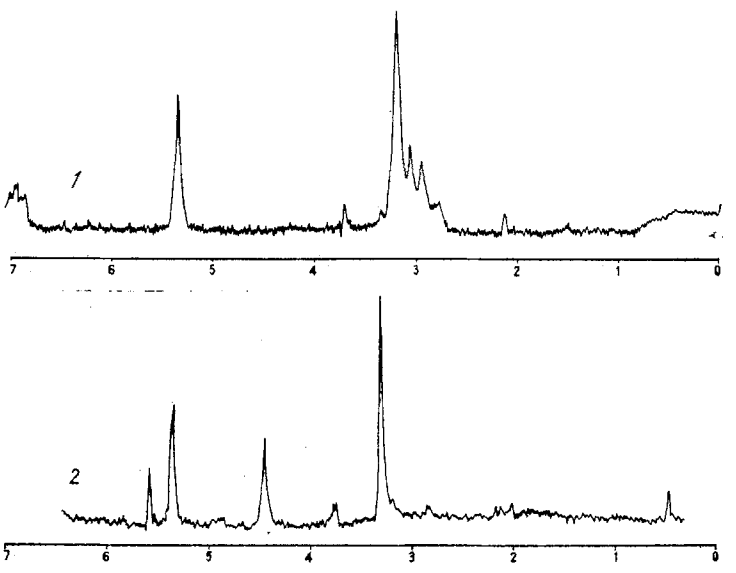


Fig. 4. PMR spectra.

For a stricter proof of the structure of the thiepinoindoles that we had obtained, we studied their PMR spectra. The PMR spectrum of substance I (Fig. 3, curve 1) has a singlet at 5.1 ppm from two equivalent protons of a benzyl methylene group attached to the indole nitrogen atom. The resonance signal at 3.8 ppm with an intensity of two proton units can be ascribed to a methylene group located between the sulfur atom and the β-position of the indole ring. In a stronger field, at 2.8–2.9 ppm, there is the signal of the four protons of two methylene groups in positions 3 and 5, split through interaction with the protons of the methylene group in position 4. In the 1.7–2.1 ppm region there is a complex multiplet of the two protons of the methylene group in position 4 due to the fact that each of these protons interacts with the four neighboring protons. The signals of the protons of the benzene nuclei of the indole moiety and the benzyl group attached to the indole nitrogen are located in the 6.7–7.3 ppm region. Substance **VII**, obtained by the condensation of phenylhydrazine and 4-thiepanone [2], has a similar PMR spectrum, with the exception of the signal at 5.1 ppm.

The spectrum of a model compound, 5-benzyl-1, 3, 4, 5-tetrahydrothiopyrano[4, 3-c]indole (**VIII**) (Fig. 3, curve 2), which we synthesized by condensing tetrahydro-4-thiopyrone and N-benzyl-N-phenylhydrazine hydrochloride has the signal of the two protons of the methylene group of the benzyl radical, a singlet signal from two protons at 3.8 ppm, which can be assigned to the protons of the methylene group in position 1 (between the β-position of the indole ring and the sulfur atom), and the signal from four protons at 2.8 ppm, which is due to the methylene groups in positions 3 and 4; the extremely close chemical shift of the protons of these two methylene groups can be explained on the basis of a similar descreening influence of the neighboring groupings.

It follows from the facts mentioned that substances I and VII each have a single methylene group between the β-position of the indole ring and the sulfur atom. Consequently, the cyclization of both primary and secondary arylhydrazones of 4-thiepanone takes place with the formation of the 1, 3, 6H-4, 5-dihydrothiepino[4, 3-c]indole system, i.e. a type A system, and substance II, obtained by the desulfonation of the thiepinoindole (I) is 1-benzyl-3-methyl-2-propylindole.

By analogy with the thiepinoindoles, it was previously [2] assumed that the S, S-dioxides of the thiepinoindoles had a structure of type B. In order to establish the structure of the products of the cyclization of primary and secondary arylhydrazones of 4-thiepanone S, S-dioxide, we performed the N-benzylation of substance **IX**, the product of the cyclization of the phenylhydrazone of 4-thiepanone S, S-dioxide. The substance so obtained proved to be identical with the product of the cyclization of the N-benzyl-N-phenylhydrazone of 4-thiepanone S, S-dioxide (**X**) [2] with respect to its R_f value on chromatography in a thin layer of alumina, its melting point, and its PMR spectrum. Consequently, the cyclization of both primary and secondary arylhydrazones of 4-thiepanone S, S-dioxide takes place, as in the case of 4-thiepanone, with the formation of substances with a single heterocyclic system. The PMR spectrum of substance **X** (Fig. 4, curve 1) has a signal of two protons of the methylene group of the benzyl radical at 5.3 ppm. A multiplet signal is present in the 2.7–3.3 ppm region, which can be assigned to the protons of four methylene groups interacting with one another in pairs. The PMR spectrum of a model compound, the S, S-dioxide of 5-benzyl-1, 3, 4, 5-tetrahydrothiopyrano[4, 3-c]indole (**XI**) [4], (Fig. 4, curve 2) has a two-proton single at 5.3–5.4 ppm, the signal of two protons at 4.4–4.5 ppm corresponding to the protons of a methylene group located between the β-position of the indole nucleus and the SO_2 group, and a signal at 3.3 ppm of four protons corresponding to two methylene groups in positions 3 and 4.

In contrast to the PMR spectrum of substance XI, that of substance X has no signal in the 4.5 ppm region which could be ascribed to the protons of the methylene group in position 1. In the 2.7–3.3 ppm region there are resonance signals with an intensity of eight proton units which we have ascribed to two methylene fragments.

Thus, substance X is 6H-6-benzyl-1, 2, 4, 5-tetrahydrothiepino[5, 4-c]indole S, S-dioxide and, consequently, belongs to the type B system in accordance with the structure previously ascribed to it [2].

We have also observed [2, 4] that in a number of cases the structure of the unsymmetrical ketones has a substantial influence on the direction of the Fischer cyclization of arylhydrazones. The present work has shown that the cyclization of arylhydrazones of 4-thiepanone and its S, S-dioxide leads to heterocycles of different structures (types A and B, respectively).

EXPERIMENTAL

The PMR spectra were taken on a INMC-60 spectrometer with a working frequency of 60 MHz in $CDCl_3$ solution. Tetramethylsilane was used as internal standard. The chemical shifts were measured on the δ scale. The IR spectra were taken on a UR-10 instrument in a thin layer between plates of KBr. The UV spectra were taken on a SF-4 instrument in ethanolic solutions with $1 \cdot 10^{-5}$–$1 \cdot 10^{-4}$ mole/l, d 1 cm.

3-Formyl-2-propylindole (V). With ice cooling, 5 ml of phosphorus oxychloride and 8 g (0.05 mole) of 2-propylindole in 20 ml of dimethylformamide were added successively in drops to 30 ml of dimethylformamide, the mixture was stirred at 35°–40° C for 1 hr and poured onto ice, 100 ml of 10% sodium hydroxide solution was added, and the mixture was heated to a boil and filtered. On cooling, the indole V crystallized from the filtrate; it was filtered off and washed with water. Yield 6.5 g (69%), mp 150°–151° C (from ethanol). Found, %: C 76.46; H 7.01; N 7.34; 7.43. Calculated for $C_{12}H_{13}NO$, %: C 76.98; H 7.00; N 7.48.

3-Methyl-2-propylindole (VI). With stirring, 2.6 g (0.06 mole) of lithium aluminum hydride in 100 ml of ethanol was added to 4 g (0.02 mole) of V in 100 ml of absolute ether, and the mixture was boiled for 18 hr. With ice cooling, it was decomposed with water, after which the ethereal layer was separated off and the aqueous layer was extracted twice with ether. The combined ethereal solution was dried and passed through a column of 40 g of alumina (activity II). Benzene eluted 2.6 g (69%) of the indole VI. Oil, n_D^{22} 1.5710. Found, %: C 82.89; 82.95; H 9.18; 9.20. Calculated for $C_{12}H_{15}N$, %: C 83.16; H 8.90.

1-Benzyl-3-methyl-2-propylindole (IV). 2.5 g (0.015 mole) of VI in 20 ml of dimethylformamide was added to 0.5 g of sodium hydride in 20 ml of dimethylformamide and the mixture was stirred at 35°–40° C for 2 hr; then 1.9 g (0.015 mole) of benzyl chloride was added and stirring was continued at 60°–80° C for 2 hr. After cooling, the reaction mixture was poured into water and extracted with ether. The extract was dried and evaporated, and the residue was distilled. The yield of the indole IV was 2 g (53%), bp 152°–155° C (0.05 mm), n_D^{23} 1.5968. Found, %: C 86.75; 86.57; H 8.29; 8.24; N 5.22; 5.54. Calculated for $C_{19}H_{21}N$, %: C 86.64; H 8.04; N 5.32.

On chromatography in a thin layer of alumina of activity II, substances IV and III gave spots with the same R_f values, namely 0.88 in benzene and 0.75 in a mixture of benzene and heptane (1:1), while on alumina of activity IV in a mixture of benzene and heptane (1:1) they had R_f 0.67.

6H-6-Benzyl-1, 2, 4, 5-tetrahydrothiepino[5, 4-c]indole S, S-dioxide (X) was obtained in a similar manner to the preceding compound from 0.6 g (0.0026 mole) of IX, 0.1 g of sodium hydride, and 0.32 g (0.0026 mole) of benzyl chloride in 25 ml of dimethylformamide. Yield 0.43 g (52%), mp 157°–159° C (from ethanol). Found, %: N 4.18; 4.32; S 10.02; 10.21. Calculated for $C_{19}H_{19}NO_2S$, %: N 4.29; S 9.82. A mixture with a sample of the indole X obtained by the Fischer reaction (mp 156°–158° C) gave no depression of the melting point. The two samples of X had similar PMR spectra and the same R_f value (0.53) on chromatography in a thin layer of alumina (activity IV) in chloroform.

5-Benzyl-1, 3, 4, 5-tetrahydrothiopyrano[4, 3-c]indole (VIII). A mixture of 2 g (0.017 mole) of tetrahydro-4-thiopyrone and 4 g (0.017 mole) of N-phenyl-N-benzylhydrazine hydrochloride in 20 ml of absolute ethanol was boiled for 20 minutes and filtered hot; VIII crystallized from the cooled filtrate. Yield 3.8 g (79%), mp 107°–108° C (from absolute ethanol). Found, %: N 4.99; 5.03; S 11.43; 11.18. Calculated for $C_{18}H_{17}NS$, %; N 5.01; S 11.48.

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