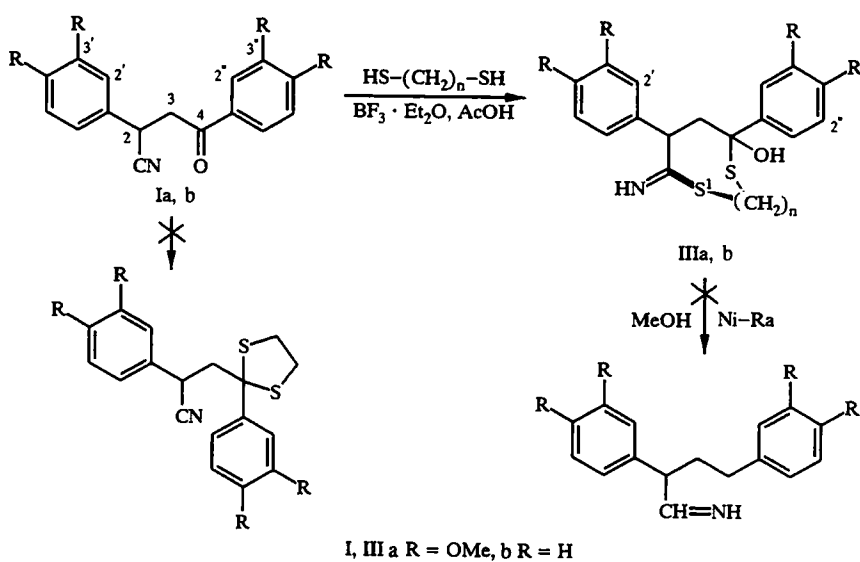


SYNTHESIS OF NEW DITHIACYCLOALKANES

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The major products of the reaction of 2,4-diaryl-4-oxobutyronitriles with dimercaptoalkanes in the presence of boron trifluoride etherate are iminohydroxydithiacycloalkanes.

2,4-Diaryl-4-oxobutyronitriles Ia and Ib obtained from the corresponding chalcones are key intermediates in the synthesis of some benzo[c]phenanthridine alkaloids and their analogs [1, 2]. In order to expand the range of applicability of oxybutyronitriles Ia and Ib, we studied their reactivity relative to nucleophilic reagents, namely, dimercaptoalkanes ($n = 2, 3$). Mercaptans II react at the carbonyl group to give dithioketals and this reaction has found use for the protection or removal of oxo groups [3, 4]. The presence of the electrophilic nitrile group in oxobutyronitrile molecules may alter the direction and lead to formation of iminohydroxydithiacycloalkanes.



These compounds may also be obtained from dimercaptoalkanes and the corresponding dihalides [5, 6].

We treated Ia and Ib with dimercaptoalkanes II ($n = 2, 3$) in the presence of a Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) in acetic acid at 20°C . The mass spectra of the dithiaalkanes obtained show strong molecular ion peaks [449 (100%) for IIIa and 343 (30%) for IIIb]. The bands for the CN and CO groups of the starting molecules are lacking in the IR spectra of these compounds, which indicates the participation of both these groups in the reaction. The IR spectrum of IIIa has bands at 3365 and 3170 cm^{-1} , which were assigned to stretching vibrations of the O-H and =N-H bonds, while the band at 1670 cm^{-1} was assigned to stretching vibrations of the C-N bond [1]. The ^{13}C NMR spectra and APT (Attach Proton Test) indicate that IIIa and IIIb have formulas $\text{C}_{22}\text{H}_{27}\text{NO}_5\text{S}_2$ and $\text{C}_{19}\text{H}_{21}\text{NOS}_2$, respectively, suggesting the presence of a single heterocycle in their structures. The existence of aromatic substituents, a polymethylene group $-(\text{CH}_2)_n-$ and isolated $-\text{CH}_2\text{CH}=\text{CH}_2$ fragment are

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indicated by PMR spectroscopy. The signals for the polymethylene group protons are found at 2.5-2.9 ppm. The signals for the methylene and methine groups of the butyryl fragment form an AMX system ($J_{AM} = 14.0$, $J_{AX} = 7.0$, and $J_{MX} = 3.5$ Hz). These signals were assigned using the COSY spectra. Thus, our data indicate that the products are iminohydroxydithiacycloalkanes IIIa and IIIb. The formation of these heterocycles should be seen as a synchronous reaction of the two electrophilic sites (carbon atoms of the carbonyl and nitrile groups) with the nucleophilic mercapto groups of IIa and IIb. The reaction products are not reduced upon heating at reflux in the presence of Raney nickel for 1 h. The use of other condensing reagents such as the catalysts employed in dithioketal protection (*p*-toluenesulfonic acid in toluene and anhydrous $AlCl_3$) as well as for the synthesis of thioimines (Et_3N and pyridine) did not lead to an increase in either the yield or reaction rate.

EXPERIMENTAL

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 45:5:0.2 chloroform-ethanol-25% aq. NH_3 . The IR spectra were taken on a Specord spectrometer for samples in Vaseline mull. The mass spectra were taken on a Varian MAT CH8 mass spectrometer at 70 eV. The NMR spectra were taken on a Varian Gemmy 200 spectrometer for solutions in $CDCl_3$ with TMS as the internal standard. A freshly distilled sample of boron trifluoride etherate was used.

A sample of 3,4,3',4'-tetramethoxychalcone was prepared in 85% yield according to Richardson et al. [9], mp 107-108°C (from 2-propanol) (mp 108°C [9]).

2,4-Diaryl-4-butyronitrilones were obtained according to Betts and Dewecy [10]. The yield of Ia was 91%, while the yield of Ib was 87%. ^{13}C NMR spectrum of Ia (APT): 31.82 ($C_{(2)}$), 44.15 ($CH_{2(3)}$), 56.13 ($O-CH_3$), 110.32 (HC_{Ar-m}), 110.48 (HC_{Ar-m}), 111.02 (HC_{Ar-o}), 111.93 (HC_{Ar-o}), 119.84 (HC_{Ar-p}), 120.90 (CN), 122.86 (HC_{Ar-p}), 127.94 ($C_{(1'')}$), 129.25 ($C_{(1'')}$), 149.26 (CO_{Ar-m}), 149.45 (CO_{Ar-m}), 149.68 (CO_{Ar-p}), 154.16 (CO_{Ar-p}), 193.32 ($C=O$).

5,7-Bis(3,4-dimethoxyphenyl)-5-hydroxy-7-imino-1,4-dithiacyclooctane (IIIa). A sample of 2 ml (20 mmoles) 1,2-dimercaptoethane and a mixture of 2 ml boron trifluoride etherate with 2 ml acetic acid were added to a solution of 1.2 g (3 mmoles) 2,4-bis(3,4-dimethoxyphenyl)-4-butyronitrilone in 15 ml acetic acid. The mixture was stirred for 72 h at room temperature, poured into water, and extracted with methylene chloride. The extract was washed with 5% aq. NaOH and saturated aq. NaCl, dried over anhydrous sodium sulfate, and evaporated to two-thirds volume. The precipitate of IIIa was separated and recrystallized from ethanol. The mother liquors were evaporated and yielded 0.42 g starting butyronitrile Ia. The yield of IIIa was 0.5 g (50%), mp 140-142°C (from ethanol). IR spectrum: 3365 ($O-H$), 3170 ($=N-H$), 1670 ($-C=N-$), 1250, 1125, 1010 cm^{-1} ($C-O-C$). PMR spectrum (COSY): 1.68 (1H, s, OH), 2.63 (1H, d.d, $J = 14$, $J = 7$ Hz, $6-H_A$), 3.18-3.30 (3H, s, CH_3), 3.35 (1H, t, $J = 7.0$ Hz, $7-H_X$), 3.52 (1H, d.d, $J = 14$, $J = 7$ Hz, $6-H_M$), 3.83, 3.84, 3.85, 3.86 ($4 \times 3H$, s, OCH_3), 5.25 (1H, s, NH), 6.66-6.78 (4H, m, H_{arom}), 7.18-7.24 ppm (2H, m, H_{arom}). ^{13}C NMR spectrum (APT): 38.88 (CH_2), 39.92 and 47.56 ($CH_{2(2,3)}$), 51.20 ($HC_{(7)}$), 56.42 ($O-CH_3$), 74.27 ($C-OH$), 110.99 (HC_{Ar-m}), 111.85 (HC_{Ar-m}), 112.00 (HC_{Ar-o}), 120.40 (HC_{Ar-o}), 120.97 (HC_{Ar-o}), 133.39 ($C_{(1'')}$), 137.16 ($C_{(1'')}$), 148.79 ($C-O_{Ar-m}$), 148.94 ($C-O_{Ar-m}$), 149.00 ($C-O_{Ar-p}$), 149.78 ($C-O_{Ar-p}$), 175.78 ppm ($S-C=NH$). Mass spectrum, m/z (I_{rel} , %): M^+ 449 (100), 359 (50), 346 (13), 313 (25), 241 (48), 195 (63), 151 (60), 124 (61). Found: C, 58.89; H, 5.98; N, 3.43%. Calculated for $C_{22}H_{27}NO_5S_2$: C, 58.80; H, 6.01; N, 3.12%.

6,8-Diphenyl-6-hydroxy-9-imino-1,5-dithiacyclononane (IIIb) was prepared as described above from 2,4-diphenyl-4-butyronitrilone and 1,3-dimercaptopropane in 47% yield relative to the starting butyronitrile consumed, mp 107-109°C (from methanol). PMR spectrum: 1.90 (2H, m, 3-H), 2.27 (1H, d.d, $J = 14.6$, $J = 3.5$ Hz, $7-H_A$), 2.70 (4H, m, 2-H, 4-H), 3.32 (1H, d.d, $J = 14.6$, $J = 7.1$ Hz, $7-H_M$), 3.45 (1H, d.d, $J = 7.1$, $J = 3.5$ Hz), $8-H_X$, 5.1 (1H, s, $=N-H$), 7.18 (9H, m, H_{arom}), 7.77 ppm (1H, d.d, H_{arom}). Mass spectrum, m/z (I_{rel} , %): M^+ 343 (30), 300 (93), 237 (100), 225 (50), 209 (43), 195 (57), 191 (50), 178 (14), 135 (70), 121 (72), 103 (100). Found: C, 66.37; H, 6.07; N, 3.85%. Calculated for $C_{19}H_{21}NOS_2$: C, 66.47; H, 6.12; N, 4.08%.

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REFERENCES

1. H. Ishii, T. Ishikawa, T. Deushi, K.-I. Haradu, T. Watanabe, E. Ueda, T. Ishida, M. Sakomoto, E. Kawanabe, T. Takahashi, Y.-I. Ishikawa, K. Takizawa, T. Masuda, and I.-S. Chen, *Chem. Pharm. Bull.*, **31**, 3024 (1983).
2. H. Ishii, T. Ishikawa, I.-S. Chen, and Y.-I. Ishikawa, *Heterocycles*, **21**, 711 (1984).
3. D. Makomi (ed.), *Protective Groups in Organic Chemistry* [Russian translation], Mir, Moscow (1976).
4. T. Soga, H. Takenoshita, M. Yamada, J. S. Han, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **64**, 1108 (1991).
5. U. K. Bandrage, L. R. Hanton, and R. A. Smith, *Tetrahedron*, **51**, 787 (1995).
6. E. Vedejs and G. A. Kraft, *Tetrahedron*, **38**, 2857 (1982).
7. S. Baldwin, *J. Chem. Soc.*, **26**, 3288 (1961).
8. L. F. Johnson and W. C. Jankowski, *Carbon-13 NMR Spectra. A Collection of Assigned, Coded, and Indexed Spectra*, Varian Associates Instrument Division, Palo Alto (1972).
9. T. Richardson, R. Robertson, and E. Seijo, *J. Chem. Soc.*, No. 4, 835 (1937).
10. B. E. Betts and W. Dewecy, *J. Chem. Soc.*, No. 11, 2606 (1958).