Heterocyclic Compounds from 3,3-Dimercapto-1-aryl-2-propen-1-ones. Note 3. Condensation with *N*-Methyl-*o*-phenylenediamine and *N*-Benzyl-*o*-phenylenediamine

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Two seven-membered ring compounds and three five-membered ring compounds were obtained by reaction in hot xylene of 3,3-dimercapto-1-phenyl-2-propen-1-one (**1**) with *N*-alkyl-*o*-phenylenediamines (**2**). Compounds isolated were the 4-phenyl-5-alkyl-1,5-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**) the 1-alkyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**4**), the 1-alkyl-2-phenacylbenzimidazoles (**5**), the 1-alkyl-2-phenylbenzimidazoles (**6**) and the 1-alkyl-2-methylbenzimidazoles (**7**). The structures of these compounds were elucidated from their chemical reactivity and their nmr and ir spectra.

In a previous paper (1) the synthesis of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione by condensation of 3,3-dimercapto-1-phenyl-2-propen-1-one (**1**) with *o*-phenylenediamine was reported.

This paper deals with the condensation of **1** with *N*-methyl-*o*-phenylenediamine (**2a**) and *N*-benzyl-*o*-phenylenediamine (**2b**). The reactions were carried out in hot xylene and two benzodiazepine derivatives, 4-phenyl-5-alkyl-1,5-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**), 1-alkyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**4**), and three benzimidazole derivatives, 1-alkyl-2-phenacylbenzimidazoles (**5**), 1-alkyl-2-phenylbenzimidazoles (**6**), and 1-alkyl-2-methylbenzimidazoles (**7**), were isolated.

Presumably 2-benzoylthioacetamido-*N*-alkylanilines and 2-[*N*-alkyl-*N*-(benzoylthioacetyl)amino]anilines are formed as intermediates in these reactions, and then undergo elimination to give, respectively **3** + **5** and **5** + **4**.

Compounds **6** and **7** can derive from **3**; in fact compounds **3** in hot xylene, if **2** was present, gave **6** and **7**. We suppose that compounds **6** are formed by contraction of the 1,5-benzodiazepine ring to the benzimidazole ring with splitting out of thioketene, which by reaction with **2** gives **7**. The compounds **4** were however unchanged under similar experimental conditions.

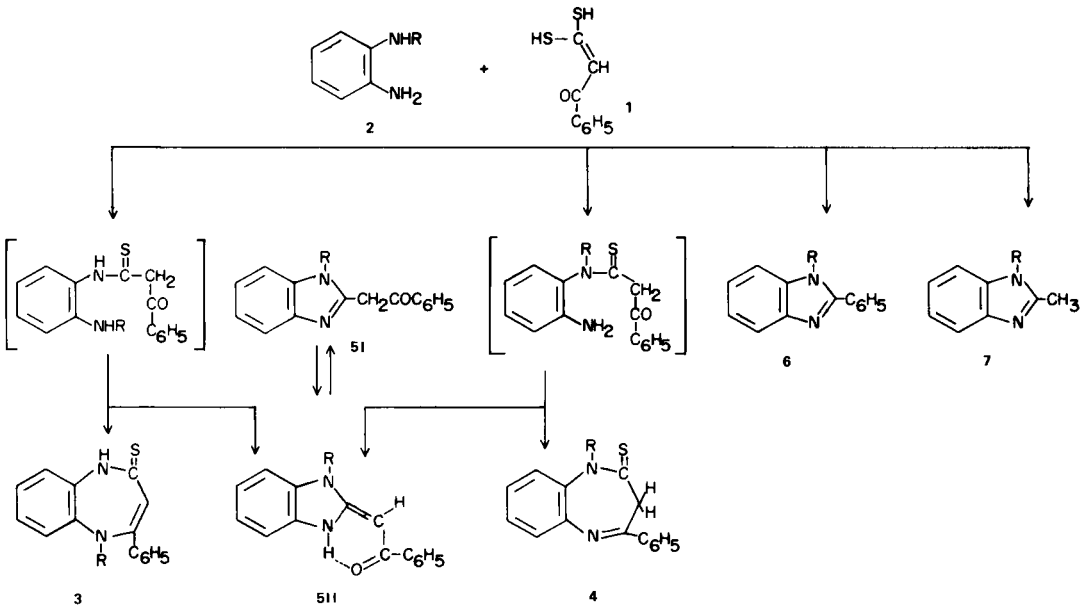
The structures of compounds obtained were elucidated from their chemical reactivity and their nmr and ir spectra.

Compounds **3**, by treatment with acetic anhydride gave 1-alkyl-2-phenyl-4-acetylthio-1*H*-1,5-benzodiazepines (**8**), and by reaction with 1-chloro-2-diethylaminoethane and sodium hydride gave 1-alkyl-2-phenyl-4-(β-diethylaminoethylthio)-1*H*-1,5-benzodiazepines (**9**). On the contrary, compounds **4** under similar experimental conditions did not give acetyl or diethylaminoethyl derivatives. The benzodiazepines **3** and **9** at room temperature by treatment with dilute hydrochloric acid contracted to the benzimidazoles **5**. In the case of **9** we observed the formation of 2-diethylaminoethyl-1-thiol (**10**), which was oxidized with iodine and identified as bis-β-diethylaminoethyl disulphide hydroiodide (**11**), which was identical to the sample prepared according to a different method reported in the literature (2). By treatment at room temperature with acetic acid, **3a** gave the stoichiometric amount of **5a**, whereas **3b** was almost unchanged and we were able to isolate only a trace of **5b**. These results support the hypothesis that the opening of the benzodiazepine ring is induced by protonation of the nitrogen atom in the 5-position. For this reason the less basic **3b** was more stable than **3a**.

The derivatives **4** were unchanged by treatment with dilute hydrochloric acid at room temperature. When the reaction was carried out at 100°, we were able to identify, beside unchanged **4**, 1-alkyl-2-phenacylbenzimidazoles (**5**), 1-alkyl-2-phenylbenzimidazoles (**6**), 1-alkyl-2-methylbenzimidazoles (**7**), and acetophenone. The formation of **6**, **7** and acetophenone is the same as we observed for acid cleavage of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (1).

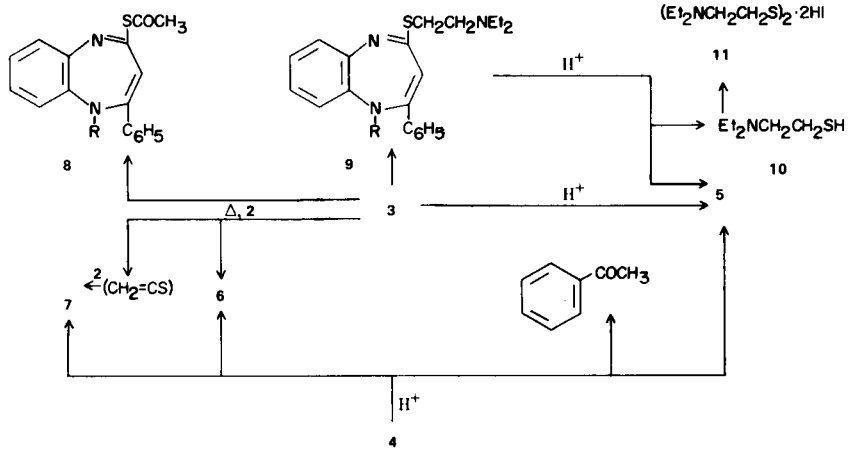
The nmr spectra of the compounds synthesized are consistent with the proposed structures. In fact we ob-

SCHEME 1



R = CH_3 (a), $C_6H_5CH_2$ (b).

SCHEME 2



served broad bands at 9.83 δ for **3a** and at 9.20 δ for **3b**, which can be attributed to the NHCS group and doublets at 5.9 δ for **3a** and 6.5 δ for **3b** related to =CH group. After deuteration the NHCS signals disappeared, whereas the =CH signals resulted as a singlet.

The nmr spectra of **4** show no signals at lower fields, but we observed an AB system (ν_A 4.78 δ, ν_B 3.26 δ, J 12 cps) for **4a** and an AB system (ν_A 4.92 δ, ν_B 3.43 δ, J 12 cps) for **4b** related to the protons of the CH_2 group, which are magnetically unequivalent. When the spectra of **4** were recorded at higher temperature, the signals tended to coalesce and resulted at 80° as a broad band. Similar observations are reported in literature for 1,4-benzodiazepine derivatives (3a,b). In the nmr spectrum of **4b** we observed also an AB system (ν_A 5.87 δ, ν_B 5.52, δ J 16 cps) which is related to the presence of two unequivalent protons of benzylic CH_2 group (3c). The nmr spectra of **5** point out the existence for these products of tautomers, analogously as we observed for 2-phenacylbenzothiazole and for 2-phenacylbenzoxazole (4).

The presence of tautomer **5I** is indicated by CH_2 signals, whereas the presence of tautomer **5II** is indicated by =CH signals (5.64 δ for **5IIa** and 5.7 δ for **5IIb**), and by NH signals (12.21 δ for **5IIa** and 10.6 δ for **5IIb**). The large paramagnetic shift of NH supports the hypothesis that an intramolecular hydrogen bond occurs between the NH

proton and the CO group. The tautomerism is confirmed also by two different signals for the NCH_3 group in the nmr spectrum of **5a**.

The tautomers **5I** occur only in solution. In fact ir spectra in the solid state are lacking the expected unconjugated carbonyl absorption bands in the range 1700-1670 cm^{-1}. The ir spectra in chloroform, however show bands at 1681 cm^{-1} which indicate that the form **5I** is present also. The ir spectra in the solid state and in solution show both bands at 1634 cm^{-1} (**5IIa**) and 1618 cm^{-1} (**5IIb**) related to carbonyl group hydrogen-bonded with NH.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus in open capillaries and are uncorrected. Nmr spectra were recorded on a Jeol C-60 HL spectrometer and chemical shifts are expressed in δ units, ppm downfield from TMS as the internal standard.

Reaction of 3,3-Dimercapto-1-phenyl-2-propen-1-one (**1**) with *N*-Methyl-*o*-phenylenediamine (**2a**).

A mixture of 98 g. (0.5 mole) of 3,3-dimercapto-1-phenyl-2-propen-1-one (**1**), 61 g. (0.5 mole) of *N*-methyl-*o*-phenylenediamine (**2a**), and 1000 ml. of xylene was stirred under a nitrogen atmosphere for 3 hours at 20-25°, then refluxed for 3 hours. After cooling, the crystals which separated were collected and recrystallized from methanol, yield, 38.9 g. (29%), m.p. 204°.

This product was identified as 4-phenyl-5-methyl-1,5-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**); nmr (deuteriochloroform): δ 3.05 (singlet, 3H, NCH_3); 5.9 (doublet, J = 2 cps, 1H, =CH), 9.83 (broad band, 1H, NHCS); after deuteration with deuterium oxide the 9.83 signal disappeared and the 5.9 signal was a singlet.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.16; H, 5.30; N, 10.52; S, 12.02. Found: C, 72.31; H, 5.19; N, 10.57; S, 12.33.

The mother liquors were evaporated under reduced pressure. Into the distillate we detected (gc, tlc) acetophenone; the residue was chromatographated on an alumina column, eluting with a mixture of petroleum ether containing an increasing per cent of benzene,benzene,benzene containing increasing per cent of methanol, and methanol. According to this procedure we were able to obtain 3.15 g. of sulphur, 20 g. (15%) of 1-methyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**4a**), and then mixtures of 1-methyl-2-phenacylbenzimidazole (**5a**), 1-methyl-2-phenylbenzimidazole (**6a**) and 1,2-dimethylbenzimidazole (**7a**) which were separated by repeated chromatographies on alumina columns providing 18.7 g. (15%) of **5a**, 10 g. (9.6%) of **6a** and 7.1 g. (9.6%) of **7a**.

1-Methyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**4a**).

This compound crystallized from ethanol 95%, m.p. 109-110°; nmr (deuteriochloroform): δ 3.75 (singlet, 3H, NCH_3), ν_a 4.78, ν_b 3.26, J 12 cps (AB system, 2H, CH_2 in 3 position).

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.17; H, 5.30; N, 10.52; S, 12.02. Found: C, 72.17; H, 5.35; N, 10.69; S, 11.90.

1-Methyl-2-phenacylbenzimidazole (**5a**).

This compound crystallized from ethanol 95°, m.p. 150-152° and was identical to the sample prepared according to the literature method (5); nmr (deuteriochloroform): δ 3.4 (singlet, 2.25 H, NCH_3 of tautomer II), 3.52 (singlet, 0.75 H, NCH_3 of tautomer I) 4.45 (singlet, 0.5 H, CH_2 of tautomer I), 5.64 (singlet, 0.75 H, =CH of tautomer II), 12.21 (broad band, 0.7 H, NH of tautomer II).

1-Methyl-2-phenylbenzimidazole (**6a**).

This compound crystallized from petroleum ether, m.p. 98°, and was identical to the sample prepared according to literature method (6).

1,2-Dimethylbenzimidazole (**7a**).

This compound crystallized from hexane, m.p. 112°, and was identical to the sample prepared according to literature method (6).

Reaction of 3,3-Dimercapto-1-phenyl-2-propen-1-one (**1**) with *N*-Benzyl-*o*-phenylenediamine (**2b**).

A mixture of 9.8 g. (0.05 mole) of 3,3-dimercapto-1-phenyl-2-propen-1-one (**1**), 9.9 g. (0.05 mole) of *N*-benzyl-*o*-phenylenediamine (**2b**), and 50 ml. of xylene was stirred under a nitrogen atmosphere for 3 hours at 20-25°, then refluxed for 3 hours. After cooling, the crystals which separated were collected and washed with petroleum ether, yield, 5.7 g. (33%), m.p. 210-212°. Crystallization from methanol gave 4.27 g. (25%) m.p. 224°. This compound was identified as 4-phenyl-5-benzyl-1,5-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3b**); nmr (deuteriochloroform): δ 4.56 (singlet, 2H, CH_2N), 6.05 (doublet, J = 2 cps, 1H, =CH), 9.2 (broad band, 1H, NHCS); after deuteration with deuterium oxide the 9.2 signal disappears and the 6.05 signal was a singlet.

Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18; S, 9.36. Found: C, 77.41; H, 5.56; N, 8.27; S, 9.57.

The mother liquors were evaporated under reduced pressure and the residue was chromatographated on a silica gel column eluting with chloroform and than with chloroform containing 2.5 per cent of ethyl acetate. According to this procedure we were able to obtain 0.15 g. of sulphur, 3 g. (17.5%) of 1-benzyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**4b**), 2.29 g. of **3b** impure of an unidentified product, 2.46 g. of a mixture of 1-benzyl-2-phenacylbenzimidazole (**5b**) and 1-benzyl-2-phenylbenzimidazole (**6b**), 3.4 g. (20%) of **5b**, 0.9 g. of a mixture of **5b** and 1-benzyl-2-methylbenzimidazole (**7b**). The mixture of **5b** and **6b** was treated with hot petroleum ether. The more soluble **6b** was separated and by crystallization from 2-propanol gave 0.5 g. (3.5%) of pure **6b**. The mixture of **5b** and **7b** was treated with ethyl ether, separating more soluble **7b**, which by crystallization gave 0.5 g. (4.5%) of pure **7b**. The 1-benzyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**4b**) crystallized from ligroin, m.p. 127-128°; nmr (deuteriochloroform): δ ν_a 5.87, ν_b 5.52, J 16 cps (AB system, 2H, CH_2Ph); ν_a 4.92, ν_b 3.43, J 12 cps (AB system, 2H, CH_2 in the 3-position).

Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18; S, 9.36. Found: C, 77.44; H, 5.39; N, 8.40; S, 9.62.

1-Benzyl-2-phenacylbenzimidazole (**5b**).

This compound crystallized from ligroin, m.p. 129-130°; nmr (deuteriochloroform): δ 5.4-4.6 (multiplet, 2.4 H, CH_2 of tautomer I and CH_2Ph), 6 (singlet, 0.8 H, =CH of tautomer II), 10.6 (broad band, 0.8 H, NH of tautomer II).

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56; N, 8.58. Found: C, 80.97; H, 5.49; N, 8.64.

1-Benzyl-2-phenylbenzimidazole (**6b**).

This compound crystallized from 2-propanol, m.p. 134°, and was identical to a sample prepared according to the literature method (7).

1-Benzyl-2-methylbenzimidazole (**7b**).

This compound crystallized from hexane, m.p. 68-69°, and was identical to a sample prepared according to the literature method (8).

1-Methyl-2-phenyl-4-acethylthio-1*H*-1,5-benzodiazepine (**8a**).

To 2.66 g. (0.01 mole) of 4-phenyl-5-methyl-1,5-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) was added 40 ml. of acetic anhydride and the mixture was stirred at 20-25° until the compound was completely dissolved. The mixture was poured into cold water, and left for several hours. The precipitate was collected, dried and crystallyzed from ethyl acetate, yield, 2.5 g. (82%), m.p. 166-169°; nmr (deuteriochloroform): δ 2.48 (singlet, 3H, $SCOCH_3$), 3.35 (singlet, 3H, NCH_3), 6.32 (singlet, 1H, =CH).

Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.11; H, 5.23; N, 9.09; S, 10.40. Found: C, 70.11; H, 5.25; N, 9.09; S, 10.38.

1-Benzyl-2-phenyl-4-acethylthio-1*H*-1,5-benzodiazepine (**8b**).

This compound was prepared from **3b** according to the above procedure. The crude product was a mixture of **3b** and **8b** which were separated by chromatography on a silica gel column eluting with chloroform. The first fraction gave 59% of unchanged **3b**, then 30% of **8b**. The product crystallized from benzene-petroleum ether with m.p. 179-182°; nmr (deuteriochloroform): δ 2.1 (singlet, 3H, $SCOCH_3$), 4.9 (singlet, 2H, CH_2N), 6.3 (singlet, 1H, =CH).

Anal. Calcd. for $C_{24}H_{20}N_2OS$: C, 74.99; H, 5.24; N, 7.29; S, 8.34. Found: C, 75.07; H, 5.52; N, 7.39; S, 8.44.

1-Alkyl-2-phenyl-4-(β-diethylaminoethylthio)-1*H*-1,5-benzodiazepines (**9**).

A mixture of 0.01 mole of **3**, 120 ml. of benzene and 0.01 mole of 50% sodium hydride in an oil dispersion was refluxed for 1 hour. Then 2.03 g. (0.015 mole) of 1-chloro-2-diethylaminoethane was added and the mixture was refluxed for 5 hours. Filtration of inorganic salt and evaporation of solvent afforded an oily residue which was warmed at 60° at 1 mm/Hg for 1 hour to eliminate 1-chloro-2-diethylaminoethane. The crude product was used for the preparation of derivatives **5**.

1-Alkyl-2-phenacylbenzimidazoles (**5**).

a) To a solution of 0.002 mole of **3** in 5 ml. of dioxane was added 5 ml. of 5*N* hydrochloric acid and the mixture was left at 20-25° for 12 days. Then sodium hydroxide was added to neutralize and the solvent was evaporated under reduced pressure. The residue was washed with water and crystallized. Yield 100%, We obtained similar results, when the reaction was carried out at 100° for 6 hours.

b) Compound **3** (0.002 mole) was suspended in 5 ml. of acetic acid and allowed to stand at 20-25° for 12 days. Compound **3a** gave a solution, whereas **3b** was almost undissolved. The mixture was poured into water and neutralized with sodium hydroxide. The precipitate was collected and crystallized. Compound **3a** gave quantitatively **5a**, whereas **3b** was unchanged. By tlc chromatography a trace of **5b** was identified.

c) The crude **9** obtained from 0.01 mole of **3** was dissolved in 50 ml. of 1*N* hydrochloric acid and allowed to stand for 20 hours at 20-25°. The red solution quickly changed to yellow. It was neutralized with sodium hydroxide, and the precipitate was collected and crystallized, yield 70-80%. The mother liquors of the reaction were titrated with 100 ml. of 0.1 *N* iodine solution to oxidize the 1-mercapto-2-diethylaminoethane (**10**) to bis-β-diethylaminoethyl disulphide (**11**). The water was evaporated *in vacuo* and the residue was extracted with hot acetone. After filtering and concentration, ether was added to crystallize bis-β-diethylaminoethyl disulphide hydroiodide, m.p. 202° (3).

Acid Cleavage of 1-Methyl-4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-thione (**4a**).

To a solution of 1.06 g. (0.004 mole) of **4a** in 12 ml. of dioxane, 6 ml. of 5*N* hydrochloric acid was added and the mixture was refluxed for 6 hours; evolution of hydrogen sulphide was observed. The solution was cooled and neutralized with dilute sodium hydroxide; the solvent was evaporated under reduced pressure, and the residue was added to water and extracted with ether. After drying and solvent evaporation the residue was washed with 5 ml. of cold methanol. The insoluble material (0.4 g., 40%) was unchanged **4a**. In the filtrate, by chromatography on a silica gel G glass plate (solvent: benzene-methanol 95:5), we identified by comparison with authentic samples: **4**, **5**, **6**, **7**, and acetophenone. The quantitative determination of **4**, **6**, and **7** was performed by tlc of a sample; the spots were scraped out and the products were eluted with methanol. By spectrophotometric reading we determined 11.7% of **4** ($E^{1\%}_{1\ cm}$ 469 λ max 265 nm), 5.3% of **6** ($E^{1\%}_{1\ cm}$ 332, λ max 287 nm) and 8.4% of **7** ($E^{1\%}_{1\ cm}$ 415, λ max 280 nm).

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