Heterocyclic Compounds from 3,3-Dimercapto-1-aryl-2-propen-1-ones. Note 1. 4-Aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones.

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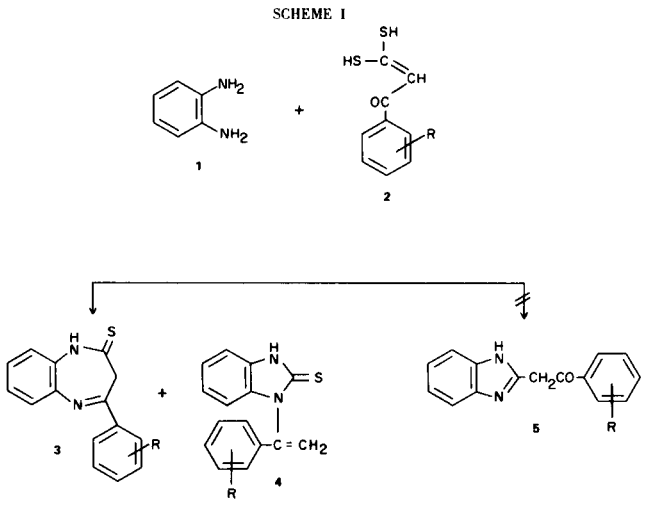
A series of new 4-aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**) has been synthesized by condensing the 3,3-dimercapto-1-aryl-2-propen-1-ones with *o*-phenylenediamine. The structure was established by the results of acid cleavage and by nmr spectra. The alkylation of compounds **3** gave 2-alkylthio-4-aryl-3*H*-1,5 benzodiazepines (**10**).

As part of our research on the preparation of heterocyclic compounds from the 3,3-dimercapto-1-aryl-2-propen-1-ones, this paper reports the synthesis of new 4-aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**), obtained by reaction of 3,3-dimercapto-1-aryl-2-propen-1-ones (**2**) with *o*-phenylenediamine (**1**).

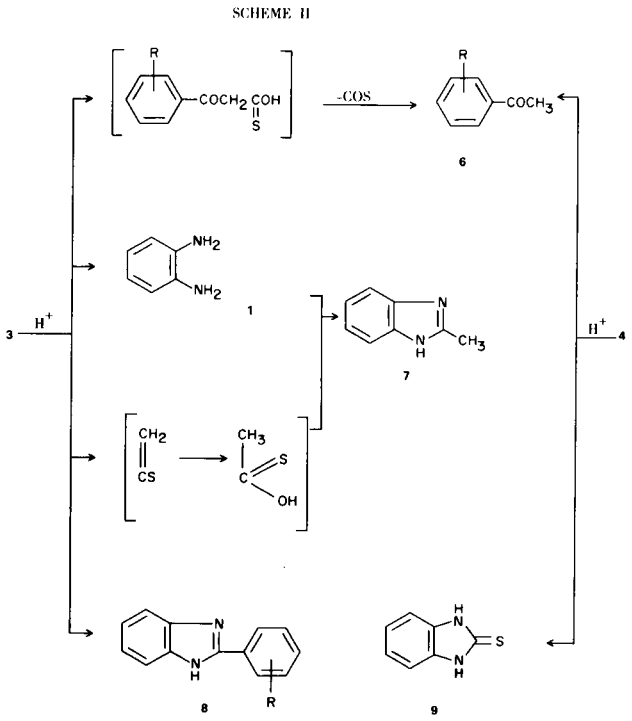
The condensation of *o*-phenylenediamine with ethyl acetoacetate or ethyl benzoylacetate has been shown to yield 4-methyl- or 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones as the major products, together with variable quantities of *N*-(α-methylvinyl)- and *N*-(α-phenylvinyl)benzimidazol-2-ones (1,2).

On the other hand, Israel *et al.* (3) reported the thermal rearrangement of 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one to *N*-isopropenylbenzimidazol-2-one and of 4-methyl-1,3-dihydro-2*H*-pyrido[2,3-*b*]-1,5-diazepin-2-one to *N*-isopropenyl-1,3-dihydro-2*H*-imidazol[4,5-*b*]pyridin-2-one. Thus, by condensing *o*-phenylenediamine (**1**) with **2** we would expect to obtain **3**, **4**, or **5** derivatives (Scheme I). In fact we always obtained derivatives of **3**.

SCHEME I



SCHEME II



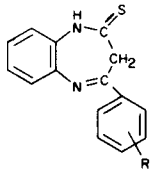
It was only in the preparation of **3b**, that we obtained as a byproduct the isomeric benzimidazole derivative **4b** which was isolated by fractional crystallization.

Structure **5** was excluded on the basis of the lack of CO stretching in the ir spectrum and for sulfur content of our products.

The structures of **3** and **4b** were established by acid cleavage and by nmr spectra.

The acid cleavage of **4b** gave 2-methoxyacetophenone and benzimidazole-2-thione (**9**), whose structure was established by elemental analysis, spectral data and comparison with an authentic sample.

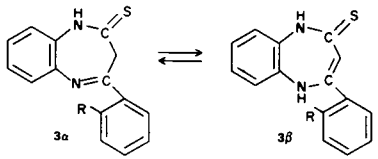
TABLE I



4-Aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**)

Compound	R	% Yield	Recryst. Solvent	M.p., °C	Formula	Calcd., % C	H	N	S	CH_3O	Found, % C	H	N	S	CH_3O
3a	H	79	AcOEt	222	$C_{15}H_{12}N_2S$	71.41	4.80	11.11	12.71		71.44	5.24	11.14	13.00	
3b	2-CH_3O	24	MeOH	197	$C_{16}H_{14}N_2OS$	68.07	5.00	9.92	11.35	10.99	67.80	5.02	9.85	11.67	11.01
3c	3-CH_3O	80	AcOEt	191	$C_{16}H_{14}N_2OS$	68.07	5.00	9.92	11.35	10.99	68.15	4.77	9.90	11.39	10.62
3d	4-CH_3O	83	AcOEt	233d	$C_{16}H_{14}N_2OS$	68.07	5.00	9.92	11.35	10.99	67.97	4.85	10.13	11.38	10.85
3e	2-CH_3	55	C_6H_6	186	$C_{16}H_{14}N_2S$	72.16	5.30	10.52	12.04		72.65	5.42	10.46	11.68	
3f	3-CH_3	74	AcOEt	205	$C_{16}H_{14}N_2S$	72.16	5.30	10.52	12.04		72.08	5.34	10.28	12.15	
3g	4-CH_3	76	AcOEt	243-245	$C_{16}H_{14}N_2S$	72.16	4.30	10.52	12.04		72.53	5.19	10.38	12.30	
3h	2-Cl	50	EtOH 95	201	$C_{15}H_{11}ClN_2S$	62.82	3.87	9.77	11.18		62.78	3.86	9.73	11.15	
3i	3-Cl	70	AcOEt	224-225	$C_{15}H_{11}ClN_2S$	62.82	3.87	9.77	11.18		63.06	3.83	9.68	11.16	
3l	4-Cl	73	AcOEt	243-245	$C_{15}H_{11}ClN_2S$	62.82	3.87	9.77	11.18		62.91	4.16	9.72	11.28	

TABLE II



NMR Data (δ) of 4-Aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**)

Compound	R	Solvent	3α N-C(=S)-CH_2 (a,b,c)	3β N-C(=S)-CH= (a,b,c)	NH (b,c)	Aromatic Protons	-CH= (d,e)	CH_2 (e)	CH_3O	CH_3
3a	H	C_6D_5N	13.70 (1H)			8.70-7.30 m (9H)		4.15 s (2H)		
		DMSO-d_6	12.50 (1H)			8.30-6.90 m (9H)		3.95 s (2H)		
3b	CH_3O	C_6D_5N	13.60 (0.75H)	11.10 (0.25H)	8.80 (0.25H)	7.80-6.80 m (8H)	6.00 ψ t (0.25H)	4.40 s (1.5H)	3.75 s (2.25H) 3.65 s (0.75H)	
		DMSO-d_6	12.38 (0.4H)	10.10 (0.6H)	8.10 (0.6H)	7.60-6.70 m (8H)	5.15 ψ t (0.6H)	3.98 s (0.8H)	3.88 s (1.8H) 3.83 s (1.2H)	
3e	CH_3	C_6D_5N	13.70 (0.5H)	11.10 (0.5H)	9.08 (0.5H)	8.40-6.90 m (8H)	5.78 ψ t (0.5H)	4.17 s (1H)		2.64 s (1.5H) 2.42s (1.5H)
		DMSO-d_6	12.50 (1H)			8.00-7.10 m (8H)		3.92 s (2H)		2.50 s (3H)
3h	Cl	C_6D_5N	13.60	11.10 (0.5H)	9.26 (0.5H)	7.80-6.90 m (8H)	5.80 ψ t (0.5H)	4.30 s (1H)		
		DMSO-d_6	12.50 (0.4H)	10.00 (0.6H)	8.40 (0.6H)	7.60-6.65 m (8H)	5.00 ψ t (0.6H)	3.95 s (0.8 H)		

(a) NH peak. (b) This peak disappears after deuteration. (c) Broad band. (d) Singlet after deuteration. (e) This peak disappears after deuteration in time.

The acid cleavage of **3** compounds gave hydrogen sulfide, *o*-phenylenediamine (**1**), substituted acetophenones (**6**), 2-methylbenzimidazole (**7**) and substituted 2-phenylbenzimidazoles (**8**), but no benzimidazole-2-thione (**9**) (Scheme II). The structures of 2-methylbenzimidazole and of substituted 2-phenylbenzimidazoles were established by elemental analysis, spectral data and comparison with the authentic samples.

o-Phenylenediamine (**1**) and substituted acetophenones (**6**) were the amjor products of acid cleavage. Presumably benzoylthioacetic acids are formed as intermediates in this reaction, but then undergo rapid elimination of COS to give derivatives **6**. We were not able to isolate benzoylthioacetic acids, which are not described in the literature. On the other hand it is reported that the analogous benzoylacetic acid undergoes decarboxylation in acid medium to give acetophenone (4).

Analogous to benzoylacetic acid, we have established that benzoylthioacetic acid in acid medium does not undergo cleavage to benzoic acid. For this reason we exclude that the substituted 2-phenylbenzimidazoles (**8**) may be formed by reaction of **1** with benzoic acids. On the contrary we propose that compounds **8** are formed by contraction of the 1,5-benzodiazepine ring to the benzimidazole ring with splitting out of CH_2=CS, which presumably affords thiolacetic acid, which by condensation with **1** gives 2-methylbenzimidazole (**7**).

In fact under our experimental conditions we were able to obtain **7** but not **8** by reaction of **1** with thiolacetic acid and benzoic acid.

It is interesting to note that Davoll (1) by acid cleavage of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11**) obtained acetophenone and 2-phenylbenzimidazole.

The nmr spectra (δ) of **3** derivatives show a singlet (4.15-4.4 in perdeuteriopyridine, 3.95-3.98 in DMSO-d_6) which may be attributed to CH_2 protons, and a broad band (13.6-13.7 in perdeuteriopyridine, 12.38-12.50 in DMSO-d_6) which may be attributed to the proton of the NHCS group of the **3**α structure. However, in the nmr spectra of some **3** derivatives we also observed the presence of peaks which suggest the presence of a **3**β-structure besides the **3**α-structure.

In fact, we also observed a pseudo triplet (=CH, 5.8-6 in perdeuteriopyridine, 5-5.15 in DMSO-d_6), a broad band (NH 8.8-9.26 in perdeuteriopyridine, 8.1-8.4 in DMSO-d_6), and a broad band (NHCCH=, 11.1 in perdeuteriopyridine, 10-10.1 in DMSO-d_6) in addition to the α-structure peaks. On addition of deuterium oxide NHCS and NH peaks disappeared, whereas the =CH peak resulted in a singlet. The CH_2 and the =CH peaks disappear at different rates in various derivatives.

Structure **3**β was more abundant when the 4-phenyl radical was substituted in the ortho position with methoxyl, methyl or chlorine (**3b**, **3e**, and **3h**).

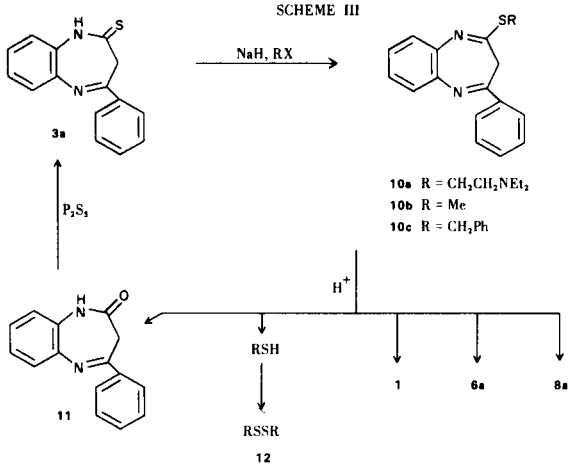
The presence of tautomers and the ratio of these tautomeric forms was dependent on the solvent used and the time the sample is in solution. The greater the length of time the sample is in solution, the more abundant the **3**β-tautomer.

The nmr spectrum of **4b** shows two singlets (5.7-6.3 in DMSO-d_6) which may be attributed to the protons of the vinyl radical in accord with Israel's observation (3) for *N*-isopropenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one. These two peaks did not occur in the spectrum of the derivatives of **3**.

We also confirmed the structure of **3a** by obtaining **3a** by the thiation of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11**) which we prepared as reported (5) by the condensation of **1** with ethyl benzoylacetate.

4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) gave by reaction with 1-chloro-2-diethylaminoethane, methyl iodide and benzyl chloride, the corresponding 2-alkylthio-4-phenyl-3*H*-1,5-benzodiazepines (**10a**, **10b**, **10c**; Scheme III).

SCHEME III



2-Diethylaminoethylthio-4-phenyl-3*H*-1,5-benzodiazepine (**10a**) by acid hydrolysis at 20-25° gave 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11**) identical with the compound obtained as described in the literature (5), and 1-mercapto-2-diethylaminoethane which was titrated with iodine solution and isolated as bis-β-diethylaminoethyldisulfidebishydroiodide (6) (**12a**)

The acid hydrolysis of **10b** and **10c** were carried out at 20-25° in aqueous alcoholic solutions because of their poor solubility in water.

Acid cleavage of **10c** gave results similar to **10a**, whereas for **10b** we observed at room temperature a more complex cleavage and we were able to isolate **1**, **6a**, and **8a** in addition to **11**.

In the experimental we also report the preparation of 2'-methoxy- and 2'-methylphenylbenzimidazoles (**8b** and

8e), which we synthesized in order to identify the products isolated after acid cleavage of **3b** and **3e**.

EXPERIMENTAL

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

4-Aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones (**3**) (Table I).

A mixture of 0.01 mole of 3,3-dimercapto-1-aryl-2-propen-1-ones (**2**), 1.08 g. (0.01 mole) of *o*-phenylenediamine (**1**) and 40 ml. of xylene was warmed at 100-110° under nitrogen for 2 hours. After cooling, the crystals were collected, washed with petroleum ether, dried and washed with water. The crude product was recrystallized.

The reaction may be carried out in benzene, toluene, alcohols, dioxane or water.

4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) from 4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11**).

A mixture of 4.72 g. (0.02 mole) of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11**) and 5.3 g. (0.024 mole) of phosphorus pentasulfide in 40 ml. of pyridine was heated under reflux for 1 hour. The reaction mixture was poured into water. The precipitate was filtered off, washed with water and dried in air. Crystallization from ethyl acetate gave 3.1 g. (60%) of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) identical (m.p., ir and nmr spectra) to the sample obtained from *o*-phenylenediamine (**1**) and 3,3-dimercapto-1-phenyl-2-propen-1-one (**2**).

Acid Cleavage of 4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**).

To a solution of 2.52 g. (0.01 mole) of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) in 30 ml. of dioxane, 15 ml. of 5 *N* hydrochloric acid were added and the mixture was refluxed for 6 hours. Evolution of hydrogen sulfide was observed. A sample of the mixture was preparatively chromatographed on a Silica Gel G glass plate (solvent system ethyl ether + petroleum ether 2:3): the spot containing acetophenone (**6**), identified by comparison with the spot of an authentic sample was eluted with methanol and the solution was read spectrophotometrically at the maximum absorbance of **6** (238 nm). The amount of **6** in the reaction mixture was 65%. The solvent was evaporated under reduced pressure and 100 ml. of water were added to the residue. The insoluble product was identified as **3a** (0.3 g., 12%). The filtrate, neutralized to *p*H 7, gave a precipitate, which was collected and identified as 2-phenylbenzimidazole (**8a**), (0.36 g. (18%)). The filtrate was evaporated to dryness and the residue extracted with hot benzene. Evaporation of the benzene solution gave 0.65 g. (60%) of **1**.

The benzene-insoluble product was extracted with hot ethyl acetate to give 0.1 g. (7.5%) of 2-methylbenzimidazole (**7**).

N,α-(2′-Methoxyphenyl)vinylbenzimidazole-2-thione (**4b**).

This compound was obtained as a byproduct in the preparation of 4-(2′-methoxy)phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3b**). The more soluble **4b** was separated by fractional crystallization from methanol, yield 18%, m.p. 188-189°; nmr (deuteriodimethylsulfoxide): δ 3.7 (3H, singlet, CH_3) 5.7 and 6.3 (2H, two single sharp lines, non equivalent methylene hydrogens) 12.8 (1H, broad band, CSNH).

Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.07; H, 5.00; N, 9.92; S, 11.35. Found: C, 67.91; H, 5.02; N, 10.00; S, 11.75.

Acid Cleavage of *N*,α-(2′-Methoxyphenyl)vinylbenzimidazole-2-thione (**4b**).

The preparation of this compound was carried out as previously described for **3a**. After evaporation of the solvent, ether was added to the residue. The insoluble product was collected and identified as benzimidazole-2-thione (**9**), 1.5 g., 100%.

Evaporation of the ether solution gave 1.4 g. (93%) of 2-methoxyacetophenone.

2-Methylthio-4-phenyl-3*H*-1,5-benzodiazepine (**10a**).

To a suspension of 2.52 g. (0.01 mole) of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) in 200 ml. of benzene, 0.48 g. (0.01 mole) of 50% sodium hydride in oil dispersion was added and the mixture was refluxed with stirring for 1 hour. Then 2.13 g. (0.015 mole) of methyl iodide was added and the mixture was refluxed for 10 hours. After cooling and filtering, the solvent was evaporated *in vacuo*. The residue was crystallized from petroleum ether, yield 1.88 g. (70%), m.p. 87-88°.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.16; H, 5.30; N, 10.52; S, 12.04. Found: C, 72.03; H, 5.42; N, 10.69; S, 11.82.

Nmr spectrum in deuteriodimethylsulfoxide: δ 2.25 (3H, singlet, SCH_3) 3.3 (2H, singlet, CH_2).

2-Benzylthio-4-phenyl-3*H*-1,5-benzodiazepine (**10b**).

This compound was obtained in a similar fashion from 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) and benzyl chloride, yield 52%. The product crystallized from petroleum ether, m.p. 88°; nmr spectrum in deuteriodimethylsulfoxide: δ 3.46 (2H, singlet, CH_2), 4.3 (2H, singlet SCH_2).

Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.17; H, 5.30; N, 8.18; S, 9.36. Found: C, 76.99; H, 5.34; N, 8.01; S, 9.48.

2-β-Diethylaminoethylthio-4-phenyl-3*H*-1,5-benzodiazepine (**10c**).

To a suspension of 2.52 g. (0.01 mole) of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**3a**) in 200 ml. of benzene, 0.48 g. (0.01 mole) of 50% sodium hydride in oil dispersion were added and the mixture 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 10 hours. After filtering, the solvent was evaporated *in vacuo* and the residue was warmed under a stream of nitrogen at 50° and 1 mm to remove the excess of 1-chloro-2-diethylaminoethane. The oily residue was dissolved in petroleum ether, filtered with charcoal and the solvent was evaporated. The crude oil was dissolved in 2-propanol and neutralized with hydrochloric acid in 2-propanol. By adding ether, the hydrochloride salt crystallized. It was filtered and recrystallized from 2-propanol-ether, yield 2.5 g. (64%), m.p. 153°.

Anal. Calcd. for $C_{21}H_{25}N_3S$·HCl: C, 65.01; H, 6.75; N, 10.83; S, 8.26. Found: C, 64.96; H, 7.01; N, 10.76; S, 8.42.

4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**11a**).

In 50 ml. of 1 *N* hydrochloric acid was dissolved 3.88 g. (0.01 mole) of 2,β-diethylaminoethylthio-4-phenyl-3*H*-1,5-benzodiazepine hydrochloride. The red solution discolours and a white product crystallized. After 5 hours the crystals were collected and recrystallized from dioxane-water to give 2.2 g. (93%) of the product, m.p. 203° (5); nmr spectrum in deuteriochloroform: δ 3.55 (2H, singlet, CH_2), 9.1 (1H, broad band, CONH); in deuteriodimethylsulfoxide: δ 3.55 (2H, singlet, CH_2) 10.5 (1H, broad band, CONH).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.11; N, 11.89. Found: C, 76.32; H, 5.25; N, 12.12.

The mother-liquor of the reaction was neutralized with sodium hydroxide solution and titrated with 97 ml. of 0.1 *N* iodine solution to oxidize the 1-mercapto-2-diethylaminoethane to bis-β-diethylaminoethyldisulphide. 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° (6).

Anal. Calcd. for $C_{12}H_{28}N_2S_2 \cdot 2HI$: S, 12.32; J, 48.78. Found: S, 12.43; J, 47.90.

2'-Amino-2-methoxybenzanilide.

A mixture of 8.16 g. (0.03 mole) of 2'-nitro-2-methoxybenzanilide in 150 ml. of methanol was hydrogenated in the presence of 0.3 g. of 10% Pd/C at atmospheric pressure and at room temperature. When the absorption of hydrogen ceased, the catalyst was filtered and the solution was evaporated. The residue was crystallized from benzene-petroleum ether, yield 6.4 g. (88%), m.p. 102°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.37; H, 5.94; N, 11.38.

2'-Amino-2-methylbenzanilide.

This compound was prepared in a similar way from 2'-nitro-2-methylbenzanilide, yield 88%; the product crystallized from benzene, m.p. 154-155°.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.53; H, 6.39; N, 12.41.

2,2'-Methoxyphenylbenzimidazole (**8b**).

A mixture of 0.484 g. (0.002 mole) of 2'-amino-2-methoxybenzanilide and 10 ml. of 5*N* hydrochloric acid was refluxed for 2 hours. After cooling, the hydrochloride salt which separated was collected and dissolved in water. The solution was made alkaline with sodium hydroxide and the precipitated base was collected, washed with water and crystallized from ethanol-water, m.p. 181°, yield 0.315 g. (70%).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.80; H, 5.40; N, 12.24.

This substance was previously obtained by other methods (7).

2,2'-Methylphenylbenzimidazole (**8e**).

This compound was prepared in a similar manner from 2'-amino-2-methylbenzanilide, yield 99%. The product crystallized from ethanol-water, m.p. 221°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.85; H, 5.64; N, 13.50.

This substance was previously obtained by other methods (7).

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