

Studies on the Syntheses of Heterocyclic Compounds. Part DII.¹ Synthesis of 1-Substituted 1,2,3,4-Tetrahydrophthalazines by a Pictet-Spengler-type Reaction of 3-Hydroxybenzylhydrazine with Carbonyl Compounds

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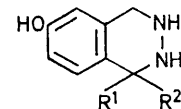
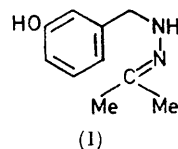
Condensations of 3-hydroxybenzylhydrazine with acetone, ethyl methyl ketone, diethyl ketone, cyclohexanone, and 1-methyl-4-piperidone in the presence of acid gave the 1,1-disubstituted 1,2,3,4-tetrahydrophthalazines (2)—(6). On the other hand, the reactions of 3-hydroxybenzylhydrazine (7) with acetone, cyclohexanone, and benzaldehyde gave the Schiff's bases (8)—(10).

WE have reported the synthesis of 1,2,3,4-tetrahydroisoquinolines from 3-hydroxyphenethylamines and carbonyl compounds by phenolic cyclisation.²⁻¹¹ In general, synthesis of many 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines by other methods is difficult. Moreover, this method has been applied to the synthesis of the alkaloid, coreximine. We now report the extension of the phenolic cyclisation reaction to the synthesis of 1,2,3,4-tetrahydrophthalazines from 3-hydroxybenzylhydrazine and various carbonyl compounds.

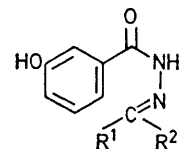
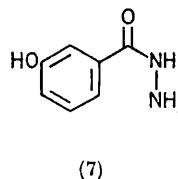
3-Hydroxybenzylhydrazine was obtained by chlorination of 3-benzyloxybenzyl alcohol¹² with thionyl chloride, and treatment of the product with hydrazine hydrate, followed by debenzoylation of the resulting hydrazine with hydrochloric acid.

Treatment of 3-hydroxybenzylhydrazine with acetone in propan-2-ol under reflux gave the Schiff's base (1) showing a positive Gibbs test and identified from u.v. (λ_{\max} , 275 nm),⁵ i.r. (ν_{\max} , 1640 cm^{-1}), and n.m.r. spectra [δ [(CD₃)₂SO] 1.70 and 1.80 p.p.m. (2 \times Me)]. However, when 3-benzyloxybenzylhydrazine hydrochloride was treated with acetone in boiling propan-2-ol saturated with hydrogen chloride gas, the expected 1,2,3,4-tetrahydro-1,1-dimethylphthalazin-6-ol (2) was obtained, showing a negative Gibbs test. The u.v. spectrum (λ_{\max} , 280 nm) revealed the presence of a substituent *para* to a hydroxy-group,⁵ and the n.m.r. spectrum (in trifluoroacetic acid) showed two methyl groups [δ 1.80 (s)] and three aromatic protons [δ 6.80 (d, *J* 2.6 Hz, 5-H), 7.12 (dd, *J* 2.6 and 9.0 Hz, 7-H), and 7.42 p.p.m. (d, *J* 9.0 Hz, 8-H)]. Heating the Schiff's base (1) with hydrochloric acid afforded the same phthalazine (2).

Analogous phthalazines (3)—(6) were obtained by heating 3-hydroxybenzylhydrazine hydrochloride with ethyl methyl ketone, diethyl ketone, cyclohexanone, and 1-methyl-4-piperidone in the presence of hydrochloric acid.



The reactions of 3-hydroxybenzylhydrazine¹³ (7) with acetone, cyclohexanone, and benzaldehyde yielded the corresponding Schiff's bases (8)—(10).¹⁴ When compound (8) was heated in 10% hydrochloric acid it gave 3-hydroxybenzoic acid, but it was unchanged when heated under reflux with pyridine and dimethylformamide.



Thus, in the condensation of 3-hydroxybenzylhydrazine with carbonyl compounds, cyclisation proceeds in the presence of acid.

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Reaction of carbonyl compounds with 3-hydroxybenzylhydrazine hydrochloride

Compd. (2)	Formula	Required (%)			Found (%)			Yield [g (%)]	Products	$\lambda_{\max.}(\text{EtOH})/\text{nm}$ (log ϵ)
		C	H	N	C	H	N			
(2)	$\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}$	67.4	7.9	15.7	67.2	8.1	15.65	0.95 (55)	Prisms (EtOH), m.p. 230° (decomp.) ^a	280 (3.24)
(3)	$\text{C}_{11}\text{H}_{16}\text{N}_2\text{O} \cdot \text{HCl}$	57.75	7.5	12.25	58.05	7.65	12.0	1.23 (55)	Needles (MeOH-Et ₂ O), m.p. >240° ^b	280 (3.18)
(4)	$\text{C}_{12}\text{H}_{18}\text{N}_2\text{O} \cdot \text{HCl}$	59.35	7.9	11.55	59.2	8.15	11.1	1.32 (56)	Needles (EtOH-Et ₂ O), m.p. 240° ^b	280 (3.27)
(5)	$\text{C}_{13}\text{H}_{18}\text{N}_2\text{O} \cdot \text{HCl}$	61.3	7.5	11.00	61.45	7.65	10.9	0.84 (34)	Needles (MeOH-Et ₂ O), m.p. >240° ^b	280 (3.13)
(6)	$\text{C}_{13}\text{H}_{19}\text{N}_3\text{O} \cdot 2\text{HCl}$	51.0	6.9	13.7	50.55	7.3	13.9	1.44 (48)	Needles (Pr ⁴ OH), m.p. 245° (decomp.) ^c	280 (3.13)

^a Free base ^b Hydrochloride ^c Dihydrochloride

EXPERIMENTAL

N.m.r. spectra were measured with a JNM-MH-60 spectrometer, with tetramethylsilane as internal reference, and i.r. spectra with Hitachi-215 recording spectrophotometer. U.v. spectra were measured with Shimadzu SV-50 and Hitachi-124 recording spectrophotometers.

3-Benzoyloxybenzyl Chloride.—A mixture of 3-benzyloxybenzyl alcohol (100 g)¹² and thionyl chloride (100 g) was refluxed for 1 h, then the excess of reagent was distilled off.

The residue was dissolved in chloroform. The extract was washed with aqueous sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated to give 3-benzyloxybenzyl chloride (105 g, 96%) as a brown oil, δ (CCl_4) 4.40 (2H, s, CH_2Cl) and 4.91 p.p.m. (2H, s, PhCH_2O).

3-Benzoyloxybenzylhydrazine.—A mixture of the foregoing chloride (100 g), hydrazine hydrate (200 g), dioxan (200 ml), and ethanol (50 ml) was refluxed for 10 h and the solvent was distilled off. To the residue was added 10% hydrochloric acid; the product was collected and recrystallised from propan-2-ol to give 3-benzyloxybenzylhydrazine hydrochloride (93 g, 82%) as needles, m.p. 143–145° (Found: C, 63.7; H, 6.15; N, 10.45. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O} \cdot \text{HCl}$ requires C, 63.5; H, 6.45; N, 10.6%).

3-Hydroxybenzylhydrazine.—A solution of 3-benzyloxybenzylhydrazine hydrochloride (4 g) in concentrated hydrochloric acid (15 ml) and ethanol (20 ml) was refluxed for 10 h, and then the ethanol was distilled off. To the residue was added water (20 ml), and the mixture was washed with ether. The aqueous layer was concentrated to give 3-hydroxybenzylhydrazine hydrochloride (1.9 g, 72%) as hygroscopic needles, m.p. 118° (decomp.) from propan-2-ol-ether (Found: C, 47.7; H, 6.55. $\text{C}_7\text{H}_{10}\text{N}_2\text{O} \cdot \text{HCl}$ requires C, 48.15; H, 6.35%), $\lambda_{\max.}(\text{EtOH})$ 275 nm (log ϵ 3.09).

Reaction of 3-Hydroxybenzylhydrazine with Carbonyl Compounds.—A mixture of 3-hydroxybenzylhydrazine hydrochloride (1.7 g), the carbonyl compound (1.0 g), and propan-2-ol (10 ml) was saturated with hydrogen chloride gas and refluxed for 10 h (see Table). Compounds (3) and (4) separated as the hydrochlorides during the reaction were recrystallised from propan-2-ol. Compound (6) precipitated on cooling the reaction mixture. Compounds (2) and (5) were obtained as free bases after treatment with 28% ammonia. The former (2) was recrystallised from ethanol and the latter (5) was converted into the hydrochloride, which was recrystallised from methanol-ether. The yields were generally in the range 34–56%.

1-(3-Hydroxybenzyl)-2-isopropylidenehydrazine (1).—A mixture of 3-hydroxybenzylhydrazine [prepared from the hydrochloride (1.7 g) by treatment with ammonia gas in propan-2-ol, followed by removal of ammonium chloride]

and acetone (1 g) was refluxed for 10 h and the solvent was evaporated to give the isopropylidenehydrazine (1) (0.52 g, 30%) as prisms, m.p. 120–122° (from acetone) (Found: C, 67.05; H, 7.55; N, 15.9. $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}$ requires C, 67.4; H, 7.9; N, 15.7%), $\lambda_{\max.}(\text{EtOH})$ 275 nm (log ϵ 3.40), δ [$(\text{CD}_3)_2\text{SO}$] 1.70 and 1.80 (3H \times 2, each s, 2 \times CH_3) and 4.13 p.p.m. (2H, s, CH_2).

1,2,3,4-Tetrahydro-1,1-dimethylphthalazin-6-ol (2).—A solution of the hydrazine (1) (100 mg) in concentrated hydrochloric acid (1 ml) was refluxed for 1 h and the reagent was distilled off to leave the phthalazine (2) hydrochloride (70 mg, 58%) as needles, m.p. >240° (from propan-2-ol-ethyl acetate), identical with an authentic sample prepared by direct cyclisation (i.r. spectral comparison).

1-(3-Hydroxybenzoyl)-2-isopropylidenehydrazine (8).—A mixture of 3-hydroxybenzoylhydrazine¹³ (7) (1.0 g), acetone (1.0 g), and propan-2-ol (10 ml) was refluxed for 2 h. The solid which separated was recrystallised from ethanol to give the isopropylidenehydrazine (8) (1.0 g, 79%) as scales, m.p. 204–207° (Found: C, 62.2; H, 6.4; N, 14.7. $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ requires C, 62.5; H, 6.3; N, 14.6%), $\nu_{\max.}(\text{KBr})$ 1660 (C=O) and 1640 cm^{-1} (C=N).

1-Cyclohexylidene-2-(3-hydroxybenzoyl)hydrazine (9).—Similar treatment of compound (7) (1.0 g) with cyclohexanone (1.0 g) in propan-2-ol (10 ml) gave the cyclohexylidenehydrazine (9) (1.3 g, 86%) as prisms, m.p. 224–226° (from methanol) (Found: C, 67.0; H, 6.95; N, 11.95. $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 67.2; H, 6.95; N, 12.05%), $\nu_{\max.}(\text{KBr})$ 1650 (C=O) and 1630 cm^{-1} (C=N).

1-Benzylidene-2-(3-hydroxybenzoyl)hydrazine (10).—A mixture of compound (7) (1.0 g), benzaldehyde (1.0 g), and propan-2-ol (10 ml) was refluxed for 2 h to give the benzylidenehydrazine (10) (1.3 g, 83%) as scales, m.p. 214–216° (from ethanol) (Found: C, 69.8; H, 5.2; N, 11.75. $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ requires C, 70.0; H, 5.05; N, 11.65%).

Reaction of 1-(3-Hydroxybenzoyl)-2-isopropylidenehydrazine (8) with 10% Hydrochloric Acid.—A mixture of compound (8) (100 mg) and 10% hydrochloric acid (3 ml) was refluxed for 1 h and cooled to give 3-hydroxybenzoic acid (40 mg, 57%) as needles, m.p. 200–201° (from water), identical with an authentic sample¹⁵ (i.r. spectral comparison and mixed m.p.).

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