897. *The Mechanism of Hydramine Fission.*

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Hydramine fission of β-hydroxyphenethylamine and some of its substitution products in presence of hydrochloric acid has been studied. The degradation products are either aromatic ketones or aldehydes. Aldehydes are formed when the phenyl nucleus is substituted in the *ortho*- or *para*-position by electron-releasing groups, whereas their *meta*-orientation or *para*- and *ortho*-substitution by electron-attracting groups favours formation of ketones, the latter being also produced from unsubstituted amine. A possible mechanism of the reaction is discussed.

β-Hydroxyphenethylamines,[1] on treatment with mineral or organic acid at elevated temperatures, split off nitrogen as amine or ammonia and are transformed into aromatic ketones. In recent years Auterhoff and Roth[2] and Fellman[3] studied the hydramine fission and showed the β-hydroxyphenethylamines, when heated with phosphoric acid, produce phenylacetaldehydes if the α-carbon is unsubstituted but that in other cases phenylacetones are the major products. Fellman[3] also predicted that similar compounds would arise from the action of 20% aqueous hydrochloric acid. The mechanism of the

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[1] Reti, in "The Alkaloids," ed. Manske, Academic Press, New York, 1953, Vol. III, p. 339; Rabe and Schneider, *Annalen*, 1909, **365**, 377.

[2] Auterhoff and Roth, *Arch. Pharm.*, 1956, **289**, 470.

[3] Fellman, *Nature*, 1958, **182**, 311.

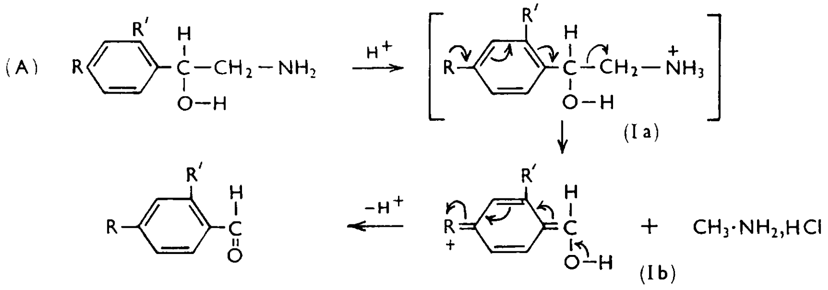
reaction has been explained by Auterhoff and Roth [2] as involving pinacol–pinacolone rearrangement.

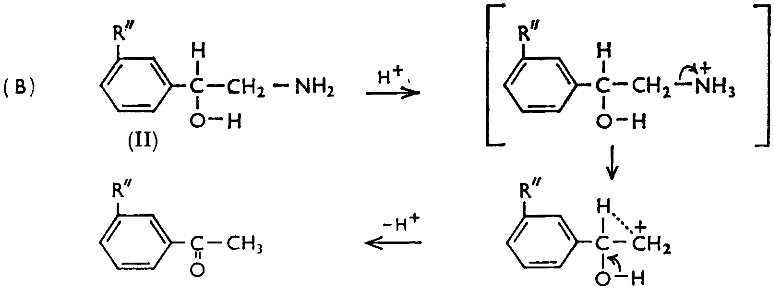
The present authors have studied the hydramine fission of various β-hydroxyphenethylamines in 10—20% hydrochloric acid. It has been observed that the nature and orientation of substituents in the phenyl nucleus play important roles in determining the course of fission. The results are set out in Table 1.

TABLE 1. *Products of fission in* HCl.

No.	β-Hydroxyphenethylamine	Product
1	4-Methoxy	*p*-Methoxybenzaldehyde
2	2-Methoxy	*o*-Methoxybenzaldehyde
3	3-Methoxy	*m*-Hydroxyacetophenone
4	4-Nitro	*p*-Nitroacetophenone
5	4-Hydroxy	*p*-Hydroxybenzaldehyde
6	3-Hydroxy	*m*-Hydroxyacetophenone
7	Unsubst.	1,3-Diphenylcyclobutadiene (*via* acetophenone)
8	4-Methyl	*p*-Methylbenzaldehyde
9	3-Methyl	*m*-Methylacetophenone

para- and *ortho*-Methoxyl, -hydroxyl, or -methyl groups greatly facilitate the hydramine fission; with *meta*-substituted or the unsubstituted amine this degradation is extremely sluggish and requires concentrated acid (which also demethylates a methoxyl group; no. 3). It seems that the mechanism is different from that proposed earlier: [2,3] when electron relay is possible, mechanism (A) operates; when this relay is not possible, transfer of electrons from the β- to the α-carbon atom cannot take place and nitrogen is eliminated as ammonia (mechanism B). In case of β-hydroxy-4-nitrophenethylamines, the hydramine fission follows path (B), resulting in the ketone; but the yield is extremely poor because of the electron-deficiency at carbon *para* to the nitro-group.





It seems that hydramine fission in presence of hydrochloric acid involves a unimolecular reaction and the formation of an 'onium ion; its kinetics are being studied. The reaction with β-hydroxyphenethylamine gave, unexpectedly, 1,3-diphenylcyclobutadiene; the predecessor of this was acetophenone which was isolated as its 2,4-dinitrophenylhydrazone when dinitrophenylhydrazine was added to reaction mixture.

EXPERIMENTAL

M. p.s were determined on a Kofler block. β-Hydroxyphenethylamines were prepared by the methods of Chaudhury and Chatterjee[4] and Corrigan *et al.*[5] with some modifications: those which did not crystallise were isolated as crystalline *N*-cinnamoyl derivatives or hydrochlorides. For hydramine fission these derivatives were employed. The yields of the carbonyl compounds were determined from those of their 2,4-dinitrophenylhydrazones (prepared *in situ*); they were 75—80% except that β-hydroxy-4-nitrophenethylamine gave only a 30% yield. Only one carbonyl derivative was isolated in each case.

Analyses were by Mr. W. Manser, Zürich, Switzerland, or Mr. B. Bhattacharya, University College of Science and Technology, Calcutta.

New *compounds* are listed in Table 2.

TABLE 2. β-*Hydroxyphenethylamines.*

Compound no. (cf. Table 1)	M. p.	Found (%) C	H	N	OMe	Formula	Required (%) C	H	N	OMe
2 (Base)	120—121°	64·6	7·6	8·5	19·0	$C_9H_{13}O_2N$	64·7	7·8	8·4	18·5
8 (Base)	68—69	71·5	8·55	9·3	—	$C_9H_{13}ON$	71·5	8·6	9·3	—
9 (Cinnamoyl deriv.)	139—140	76·6	6·5	4·9	—	$C_{18}H_{19}O_2N$	76·8	6·8	4·9	—

β-*Hydroxy-3-methoxyphenethylamine.*—ω-Bromo-3-methoxyacetophenone[6] (13 g.) was converted into its hexamethylenetetramine derivative in dry monochlorobenzene (29 ml.) at 50—52°. This was decomposed with alcoholic hydrochloric acid into the ω-amino-ketone, isolated as its crystalline hydrochloride (5·3 g.) which with sodium borohydride (6 g.) in dry methanol (200 ml.) afforded oily β-hydroxy-3-methoxyethylamine (2 g.). The *cinnamate* (3 g.) crystallised from ethyl acetate in needles, m. p. 131—132° (Found: C, 72·3; H, 6·5; N, 4·6. $C_{18}H_{19}O_3N$ requires C, 72·2; H, 6·7; N, 4·7%).

The *compounds* listed in Table 3 were prepared analogously.

TABLE 3. *Further* β-*hydroxyphenethylamines.*

Compound no. (see Table 1)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
4 (Base)	136—137°	52·8	5·4	15·2	$C_8H_{10}O_3N_2$	52·7	5·5	15·3
5 (Hydrochloride)	167—169	50·7	6·4	7·5	$C_8H_{11}O_2N,HCl$	50·6	6·3	7·4
6 (Hydrochloride)	157—158	50·7	6·4	7·5	$C_8H_{11}O_2N,HCl$	50·6	6·3	7·4
7 (Cinnamoyl deriv.)......	176—178	76·45	6·4	5·3	$C_{17}H_{17}O_2N$	76·4	6·3	5·2

Hydramine Fissions.—*N*-(β-Hydroxy-3-methoxyethyl)cinnamamide (0·5 g.) was heated at 120° for 4 hr. in a sealed tube with 50% alcoholic hydrochloric acid (5 ml.). The mixture was then diluted with a little water and extracted with ether (3 × 15 ml.). The ethereal layer was freed from acid and was dried (Na_2SO_4). The residue left after removal of the solvent furnished anisaldehyde 2,4-dinitrophenylhydrazone which crystallised from ethyl acetate in red flakes, m. p. 250° (Found: N, 17·9. Calc. for $C_{14}H_{12}N_4O_5$: N, 17·7%).

Fission of compounds 2—6, 8, and 9 was carried out similarly with minor variations (see Tables 1 and 4).

Fission of N-(β-*Hydroxyphenylethyl*)*cinnamamide.*—The amide (0·5 g.) was heated with concentrated hydrochloric acid (7 ml.) and 2,4-dinitrophenylhydrazine (0·4 g.) in a sealed tube at 130—135° for 4 hr. Cooling and filtration then gave a reddish-orange residue that crystallised from glacial acetic acid in needles, m. p. 236—237° alone or mixed with acetophenone 2,4-dinitrophenylhydrazone (Found: C, 56·2; H, 4·2; N, 18·7. Calc. for $C_{14}H_{12}O_4N_4$: C, 56·0; H, 4·0; N, 18·7%).

When β-hydroxyphenethylamine had been heated with 20% aqueous hydrochloric acid alone at 120—130° for 15 hr., working up as described above gave 1,3-diphenylbutadiene that crystallised in good yield from alcohol in plates, m. p. and mixed m. p. 97—98° (Found: C, 94·2;

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[4] Chaudhury and Chatterjee, *J. Indian Chem. Soc.*, 1959, **36**, 585.
[5] Corrigan, Langerman, and Moore, *J. Amer. Chem. Soc.*, 1945, **67**, 1894.
[6] *Org. Synth.*, 1947, Coll. Vol. II, p. 480.

TABLE 4. *Fission products* (cf. Table 1).

Amine no. (cf. Table 1)	HCl (%)	Temp.	Time (hr.)	2,4-Dinitrophenylhydrazone of product			
				M. p.	N (Found, %)	Formula	N (Calc., %)
1 (Cinnamoyl deriv.) ...	10	120°	4	250°	17·9	$C_{14}H_{12}O_5N_4$	17·7
2 (Base)	20	120	15 or 10	237—239	17·7	,,	17·7
3 (Cinnamoyl deriv.) ...	20	130—140	65	239—240	17·9	,,	17·7
4 (Base)	20	120	60	255	20·45	$C_{14}H_{11}O_6N_5$	20·3
5 (Hydrochloride)	10	120	15	280	18·6	$C_{13}H_{10}O_5N_4$	18·5
6 (Hydrochloride)	20	130	65	240	17·8	$C_{14}H_{12}O_5N_4$	17·7
7 (Cinnamoyl deriv.) ...	20	120	4	236—237	18·7	$C_{14}H_{12}O_4N_4$	18·7
8 (Hydrochloride)	10	120	15	233	18·8	,,	18·7
9 (Hydrochloride)	20	130	65	207	17·9	$C_{15}H_{14}O_4N_4$	17·8

H, 5·85%; *M*, 202. Calc. for $C_{16}H_{12}$: C, 94·1; H, 5·9%; *M*, 204), $\lambda_{max.}$ 249 (log ε 3·15) and 287·5 mμ (log ε 4·22) in EtOH.

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