Reducing Action of Glycols in Alkaline Medium. Part I. Mechanism of Formation of Stilbenes from Substituted Benzaldehydes.

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Stilbenes, alcohols, and acids are formed when substituted benzaldehydes are heated with sodium dissolved in ethylene glycol. Neither hydrobenzoins nor deoxybenzoins are intermediates in the formation of stilbenes. The alcohols were also obtained by reducing the aldehydes with lithium aluminium hydride.

Anisoin, hydroanisoin, and deoxyanisoin are excluded as intermediates in the formation of 4 : 4′-dimethoxystilbene from *p*-anisaldehyde by alkaline ethylene glycol (Tadros and Ekladius, *Nature*, 1950, **166**, 525). Hydroanisoin was recovered unchanged after several hours' refluxing. Deoxyanisoin gave mainly 1 : 2-di-*p*-methoxyphenylethanol and *p*-hydroxyphenyl 4-methoxybenzyl ketone. The structure of the latter product was proved by comparison of the ethylation products with the two possible isomers synthesised by Friedel–Crafts reactions with stannic chloride (Wilds and Biggerstaff, *J. Amer. Chem. Soc.*, 1845, **67**, 789; see also Carter and Hey, *J.*, 1948, 150), and by degradation of the ethylated ketone by fusion with sodium hydroxide to *p*-ethoxybenzoic acid.

On similar treatment anisoin gave hydroanisoin and a little deoxyanisoin. Anisil was obtained when anisoin was heated in alkaline glycerol (Tadros and Ekladius, *loc. cit.*).

o- and *m*-Alkoxy- and *p*-dimethylamino-benzaldehydes gave also the corresponding stilbenes, alcohols, and acids. The alkoxybenzyl alcohols were also obtained by reduction of the aldehydes with lithium aluminium hydride.

When injected subcutaneously in sesame oil into 5 ovariectomised 22-g. mice, 4 : 4′-bisdimethylaminostilbene (dose, 5 mg. in 0·4 c.c.; 4 × 0·1 c.c. during 2 days) had no œstrogenic activity.

Experimental

Action of Sodium 2-Hydroxyethoxide in Glycol on Substituted Benzaldehydes.—The procedure and products obtained are exemplified by the following. Anisaldehyde (16·8 g., 0·1 mol.) and a solution of sodium (1·4 g., 0·06 g.-atom) or sodium hydroxide (2·4 g., 0·06 mol.) in ethylene glycol (30 c.c.) were refluxed for 3·5—4 hr. The mixture was diluted with water, and the precipitate was filtered off. Recrystallisation from acetic acid or benzene gave colourless 4 : 4′-dimethoxystilbene, m. p. 214° (1·25 g.). The acetic acid or benzene mother-liquors contained an unidentified resin (8 g.). The turbid alkaline filtrate was extracted with ether. Ether was left to evaporate at room temperature and the residue was crystallised from light petroleum (b. p. 50—60°) from which anisyl alcohol, m. p. 25°, separated [*p*-nitrobenzoate, m. p. and mixed m. p. 93—94° (Mozingo and Folkers, *J. Amer. Chem. Soc.*, 1948, **70**, 229)]. Acidification of the alkaline solution with hydrochloric acid gave anisic acid, m. p. and mixed m. p. 184°.

Other *stilbenes* (yield, 6—8%) (see Table 1) crystallised from acetic acid, benzene, or toluene and were colourless except the bisdimethylamino-compound (pale yellow). The alcohols (yield, 8—10%; also obtained quantitatively by reducing the aldehydes with lithium aluminium hydride, see below) and the acids (yield, 4%) are reported in Table 2.

Products obtained from Deoxyanisoin.—Deoxyanisoin (6 g.) and sodium (0·7 g.) in ethylene glycol (15 c.c.) were refluxed for 3 hr. On dilution with water 1 : 2-di-*p*-methoxyphenyl-

TABLE 1. *Stilbenes*, $C_6H_4R{\cdot}CH{:}CH{\cdot}C_6H_4R$.

R	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
o-MeO [a, b]	136°	79·6	6·5	$C_{16}H_{16}O_2$	80·0	6·7
m-MeO [b, c]	98	79·3	6·3	$C_{16}H_{16}O_2$	80·0	6·7
p-MeO [a–h]	214	80·0	6·5	$C_{16}H_{16}O_2$ *	80·0	6·7
o-EtO [b]	88	80·2	7·7	$C_{18}H_{20}O_2$	80·6	7·5
p-EtO [b, d, h, i]	207	80·0	7·3	$C_{18}H_{20}O_2$	80·6	7·5
p-Pr^{n}O [j]	194—195	81·0	8·1	$C_{20}H_{24}O_2$	81·1	8·1
p-Pr^{i}O	145	80·8	8·0	$C_{20}H_{24}O_2$	81·1	8·1
p-Bu^{n}O	187	81·7	9·1	$C_{22}H_{28}O_2$	81·5	8·6
p-*n*-$C_5H_{11}O$	174	82·1	8·8	$C_{24}H_{32}O_2$	81·8	9·1
p-*n*-$C_7H_{15}O$	158—159	82·3	9·2	$C_{28}H_{40}O_2$	82·4	9·8
p-*n*-$C_8H_{17}O$	155	82·2	10·1	$C_{30}H_{44}O_2$	82·6	10·1
p-Me_2N [k]	260	80·4	8·0	$C_{18}H_{22}N_2$ †	81·2	8·3

* Found : MeO, 25·0. Calc. : MeO, 25·0%. † Found : N, 9·7. Calc. : N, 10·5%.

[a] Kopp, *Ber.*, 1892, **25**, 600. [b] Pascal and Normand, *Bull. Soc. chim.*, 1911, **9**, 1059. [c] Kopp, *Annalen*, 1893, **277**, 339. [d] Wiechell, *ibid.*, 1894, **279**, 337. [e] Brand and Matsui, *Ber.*, 1913, **46**, 2942. [f] Stobbe and Hensel, *Ber.*, 1926, **59**, 2254. [g] Sah and Yuin, *Chem. Abs.*, 1947, **41**, 5869. [h] Brand, *Ber.*, 1913, **46**, 2935. [i] Frankforter and Kritchevsky, *J. Amer. Chem. Soc.*, 1914, **36**, 1511. [j] Also prepared (Tadros and Aziz) by refluxing a benzene (50 c.c.) solution containing 2 : 2 : 2-trichloro-1 : 1 : di-(*p*-*n*-propoxyphenyl)ethane (Stephenson and Waters, *J.*, 1946, 339) (0·6 g.) and powdered sodium (0·1 g.) for 16 hr.; filtration and concentration gave the stilbene, m. p. and mixed m. p. 194—195°. [k] Campaigne and Budde, *Chem. Abs.*, 1950, **44**, 4478, give m. p. 253—254°. The *n*-propoxy- to *n*-octyloxy-stilbenes are new.

TABLE 2.

Substituent	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Benzyl alcohols.						
m-MeO [a]	29—30°	69·4	7·5	$C_8H_{10}O_2$	69·6	7·2
3 : 5-dinitrobenzoate [b]	120—121	N, 9·1		$C_{15}H_{12}O_7N_2$	N, 8·4	
o-EtO [c]	31—32	71·0	7·4	$C_9H_{12}O_2$	71·1	7·9
3 : 5-dinitrobenzoate [b]	109	N, 8·1		$C_{16}H_{14}O_7N_2$	N, 8·1	
p-EtO [d]	27	71·2	7·7	$C_9H_{12}O_2$	71·1	7·9
p-Pr^{n}O [e]	28—29	72·7	8·8	$C_{10}H_{14}O_2$	72·3	8·4
p-Pr^{i}O	27—28	71·7	8·5	$C_{10}H_{14}O_2$	72·3	8·4
p-Bu^{n}O	30—31	73·0	8·8	$C_{11}H_{16}O_2$	73·3	8·9
p-n-$C_5H_{11}O$	33	74·0	9·3	$C_{12}H_{18}O_2$	74·2	9·3
p-*n*-$C_7H_{15}O$	48	76·5	10·0	$C_{14}H_{22}O_2$	75·7	10·0
p-*n*-$C_8H_{17}O$	49	76·3	10·0	$C_{15}H_{24}O_2$	76·3	10·2
p-Me_2N methiodide	232	41·6	5·7	$C_{10}H_{16}ONI$ *	41·0	5·5
Benzoic acids. [f]						
p-EtO	195	65·1	6·4	$C_9H_{10}O_3$	65·1	6·0
p-Pr^{n}O	141—142	66·0	6·5	$C_{10}H_{12}O_3$	66·7	6·7
p-Pr^{i}O	163	66·6	6·0	$C_{10}H_{12}O_3$	66·7	6·7
p-Bu^{n}O	145—146	67·3	7·0	$C_{11}H_{14}O_3$	68·0	7·2
p-*n*-$C_5H_{11}O$	122	68·8	7·4	$C_{12}H_{16}O_3$	69·2	7·7

* Found : N, 4·8. Calc. : N, 4·8%.

[a] Pschorr (*Annalen*, 1912, **391**, 40) gives b. p. 252°. [b] These dinitrobenzoates were obtained by heating the alcohol (0·5 g., 1·25 ml.), 3 : 5-dinitrobenzoyl chloride (0·7 g., 1 mol.), and a few drops of pyridine on the water-bath for 30 min., and crystallisation from light petroleum (b. p. 50—60°). [c] Pschorr and Zeidler (*ibid.*, 1910, **373**, 75) give b. p. 254°. Bötsch (*Monatsh.*, 1880, **1**, 621) gives b. p. 264°. Hart and Hirschfelder (*J. Amer. Chem. Soc.*, 1921, **43**, 1688) give b. p. 264°/760 mm., 149—150°/28 mm. [d] Braun and Michaelis (*Annalen*, 1933, **507**, 1) give b. p. 134—135°/12 mm. [e] Smith and Burnett, jun. (*Chem. Abs.*, 1950, **44**, 6569) give no details. [f] These acids had m. p.s unchanged on admixture with samples prepared by Jones's method (*J.*, 1935, 1874; see also Cohen and Dudley, *J.*, 1910, 1732). *o*-Ethoxybenzoic acid was identified as the amide, m. p. and mixed m. p. 110° (Limpricht, *Annalen*, 1856, **98**, 256). *m*-Methoxy-, m. p. 105—106° (Graebe, *ibid.*, 1905, **340**, 204) and *p*-dimethylamino-benzoic acid (Zaki and Tadros, *J.*, 1941, 562) had m.p.s unchanged on admixture with authentic samples. *p*-Heptyloxy- and *p*-octyloxy-benzoic acid were obtained in very small quantities.

ethanol separated and was filtered off. It had m. p. 110° (0·8 g.) (from dilute acetic acid) (Found : C, 74·2; H, 6·8. Calc. for $C_{16}H_{18}O_3$: C, 74·4; H, 7·0%). Heating the alcohol with concentrated hydrochloric and acetic acid (Buck and Jenkins, *J. Amer. Chem. Soc.*, 1929, **51**, 2163) gave 4 : 4′-dimethoxystilbene, m. p. and mixed m. p. 214°. The alkaline filtrate afforded p-*hydroxyphenyl* 4-*methoxybenzyl ketone* (0·7 g.), m. p. 175° (from dilute alcohol) (Found : C, 74·4; H, 5·8; OMe, 13·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; OMe, 12·8%).

p-*Ethoxyphenyl* 4-*Methoxybenzyl Ketone*.—(*a*) *p*-Methoxyphenylacetyl chloride (from 1·25 g. of acid; Carter and Hey, *loc. cit.*) in thiophen-free benzene (6 c.c.) and dry phenetole (3·2 c.c.), cooled in ice, was treated with a mixture of anhydrous stannic chloride (2·5 c.c.) and dry benzene (2·5 c.c.), left for 12 hr., then hydrolysed with ice and hydrochloric acid and extracted with ether. The solvent was removed and the residual *ketone* crystallised from alcohol as colourless crystals, m. p. 101—102° (0·8 g.) (Found : C, 75·6; H, 6·6. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%).

4-*Ethoxybenzyl* p-*methoxyphenyl ketone*, similarly prepared, and crystallised from alcohol, had m. p. 100° (0·8 g.) (Found : C, 75·6; H, 6·6%).

(*b*) *p*-Hydroxyphenyl 4-methoxybenzyl ketone (0·5 g.) in alcoholic sodium methoxide (0·05 g. of sodium in 15 c.c. of alcohol) was refluxed for 15 min. Ethyl iodide (1·2 g.) was added and the mixture was refluxed for a further 1·5 hr., then evaporated. The residue, washed with water to remove the sodium iodide and crystallised from alcohol, had m. p. 102° (0·5 g.), alone or mixed with *p*-ethoxyphenyl 4-methoxybenzyl ketone prepared as above, but depressed on admixture with the isomer.

Degradation of the Ketones.—The ketone (0·1 g.) was added to fused sodium hydroxide (0·2 g.) and carefully heated for 0·5 min. The material was dissolved in hot water and filtered, and the filtrate was acidified. The precipitated acids were recrystallised from dilute alcohol. *p*-Ethoxyphenyl 4-methoxybenzyl ketone, obtained by either method, gave *p*-ethoxybenzoic acid, m. p. and mixed m. p. 195°. 4-Ethoxybenzyl *p*′-methoxyphenyl ketone gave *p*-anisic acid, m. p. and mixed m. p. 181°.

Reduction of Anisoin.—Anisoin (10 g.) was refluxed with sodium (2·3 g.) in ethylene glycol (30 c.c.) for ½ hr. Hydroanisoin (2·4 g.), m. p. and mixed m. p. 168°, and deoxyanisoin (0·36 g.), m. p. and mixed m. p. 109—110°, were precipitated on dilution and were separated by fractional crystallisation from alcohol. When heating was for 3½ hr., 4 : 4′-dimethoxystilbene (0·017 g.), m. p. and mixed m. p. 214°, was also obtained.

Oxidation of Anisoin.—Anisoin (10 g.) and sodium (2·4 g.) in glycerol (30 c.c.) were heated at 190—195° for 1½ hr. Dilution and crystallisation from alcohol gave anisil (1 g.), m. p. and mixed m. p. 133° (monoxime, m. p. 131°). On concentration of the alcoholic mother-liquor, unchanged anisoin was recovered.

Reductions by Lithium Aluminium Hydride.—These are exemplified by the following. To an ice–salt-cooled solution of *p*-anisaldehyde (1·36 g., 1 mol.) in dry ether (50 c.c.), powdered lithium aluminium hydride (1·52 g., 4 mol.) was gradually added. The mixture was then refluxed for 1 hr. Excess of lithium aluminium hydride was decomposed by water, added dropwise to the cooled mixture. Dilute acetic acid (1 : 1; 50 c.c.) was added and the ethereal layer was washed with aqueous sodium carbonate and then water. The ethereal solution was dried (Na_2SO_4) and ether was removed. 4-Methoxybenzyl alcohol, crystallised from light petroleum (b. p. 50—60°), had m. p. and mixed m. p. 24—25° (1·35 g.).

2-Methoxybenzyl alcohol was identified as the *p*-nitrobenzoate, m. p. and mixed m. p. 81—82° (Mozingo and Folkers, *loc. cit.*).

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