119. *The Influence of Substituents on the Reactivity of the Hydroxyl Group in β-Phenylethyl Alcohol.*

By G. M. Bennett and Mostafa Mahmoud Hafez.

A series of substituted β-phenylethyl alcohols with substituents in the *o*- and *p*-positions has been prepared and their reactivities with hydrobromic acid examined in order to discover which atoms or groups cause the special activity of hydroxyl previously found in the open-chain δ-hydroxy-sulphides. The alcohol with the methylthio-group, CH_3·S–, in the *o*-position reacts 620 times as fast as its *p*-isomeride, but several other substituents show no such effect. A similar effect of the amino-group, which might be expected, could not be demonstrated by means of the reaction with hydrobromic acid owing to salt formation. A high reactivity of the hydroxyl group in *o*-amino-β-phenylethyl alcohol is nevertheless displayed in a remarkable reaction which it undergoes with arylsulphonyl chlorides. This readily yields the cyclic base indoline, and the mechanism of this process is discussed. o-*Methylthio*-β-*phenylethyl alcohol* reacts with hydrochloric acid at the same speed as with hydrobromic acid, a fact which throws light on the nature of the reaction.

In previous papers (Bennett and Mosses, J., 1931, 2956; Bennett and Reynolds, J., 1935, 131) a study was made of the velocity of reaction of a number of alcohols with hydrobromic acid in phenolic solution, and a greatly enhanced reactivity was found in compounds having in the molecule a sulphur atom separated from the hydroxyl group by a chain of four saturated carbon atoms, that is to say, in δ-hydroxy-sulphides R·S·$[CH_2]_4$·OH.

In the present communication we describe an investigation of some substituted β-phenylethyl alcohols with substituents in the *o*- and *p*-positions. As the substituent in the *o*-position in these alcohols is separated by four atoms from the hydroxyl group, any activating effects of the kind previously detected should become apparent, the *p*-isomeride providing in each case a standard against which to judge the extent of the effect.

The substituted phenylethyl alcohols were prepared from the *o*- and *p*-amino-β-phenylethyl alcohols by methods requiring, in general, no comment. A surprising reaction was, however, discovered when the *o*-amino-alcohol was shaken with *p*-toluenesulphonyl chloride and aqueous alkali with the object of preparing the arylsulphonamido-alcohol. The product isolated was insoluble in alkali and proved to be the *p*-toluenesulphonyl derivative of the cyclic base indoline (dihydroindole). This reaction must depend on a high reactivity of the hydroxyl group and will be discussed later (p. 655). When the parent alcohol was dissolved in pyridine the arylsulphonyl chloride acted upon it normally to give the required arylsulphonamido-alcohol, which dissolved in alkali in the usual manner.

Following the experimental method described in previous communications, we have examined the velocities of reaction of these alcohols with hydrobromic acid in phenol solution. The results are in the following table.

Velocities of Reaction of Substituted Alcohols, $C_6H_4X{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, *with Hydrobromic Acid at* 80° : k × 10^4.

X =	NO_2	$Me{\cdot}SO_2$	H	I	SMe	$Ph{\cdot}SO_2{\cdot}NH$	OMe
p-	1·65	4·35	(5·90)	6·9	11·0	54·0	106
o-	3·10	3·20	(5·90)	3·25	6,840	43·0	35·0

The coefficients *k* have been calculated by means of the general equation for a reversible second-order reaction, but in the case of the nitro- and iodo-alcohols the ordinary equation for an irreversible reaction was used, since the observations did not extend over any large fraction of the complete reaction and the two equations give almost identical results (compare Bennett and Reynolds, *loc. cit.*).

The figure for the *o*-MeS compound is approximate, having been computed by extrapolation from two observations at 30° and 40°. There is moreover some uncertainty as to the kinetics of this activated reaction, which probably has its own mechanism (see p. 654). There is no doubt, however, that the *o*-methylthio-alcohol reacts about 600 times as rapidly with hydrobromic acid as does its *p*-isomeride. At the same time the activation energy is approximately 22,000 cals. in both cases.

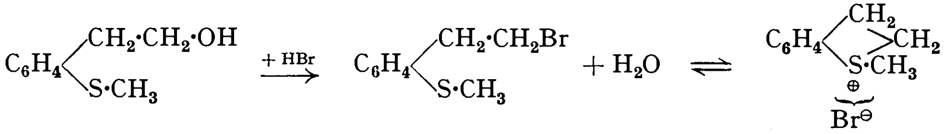
The figures for the *p*-substituted alcohols show comparative reactivities increasing with various substituents in the following series: $NO_2 < Me{\cdot}SO_2 < H < I < SMe < Ph{\cdot}SO_2{\cdot}NH < OMe$. The sequence is consistent with the known inductive effects of these atoms and groups, and the classification of the reaction as one retarded by electron recession, and needs no further discussion.

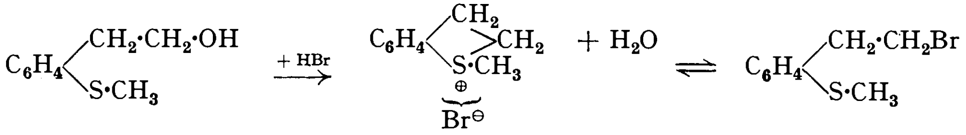
A comparison of the figures for the *o*- and *p*-isomerides reveals no striking difference of reactivity except in the case of the methylthio-group. The ratio of the velocities of reaction of these two substances is even higher than that found for the alcohols of the structures $C_6H_5{\cdot}S{\cdot}[CH_2]_4{\cdot}OH$ and $C_6H_5{\cdot}S{\cdot}[CH_2]_{10}{\cdot}OH$. This is in agreement with the view previously advanced that the enhanced reactivity depends on the ready approach of the sulphur atom to the $CH_2{\cdot}OH$ group in the former substance. The rigid structure of the group $CH_2{\cdot}C_6H_4{\cdot}SMe$ of *o-methylthio-β-phenylethyl alcohol* must make the mutual approach of carbinol group and sulphur atom more easy than was the case with the open-chain hydroxy-sulphide in which four methylene groups intervene between sulphur and hydroxyl with freedom of rotation at every point.

These results give a clear indication of the nature of the action of the activating group SMe. The characteristic of this group is that it possesses on the sulphur atom lone pairs of electrons known to be available for covalency formation with alkyl radicals. If the effect were exactly parallel with the basic function of the group, the methoxy-group should be more effective than the methylthio-group; but it is not, indeed there is no certain indication of any special activity in *o-methoxy-β-phenylethyl alcohol.* If the mere possession, by the atoms of the substituent, of lone pairs of electrons were the essential factor, the iodine atom or the nitro-group should show such effects; but they do not. It seems, therefore, that the influence under discussion depends on the capacity of the sulphur atom to pass into the 3-covalent condition by sharing a lone pair of electrons with another carbon atom.

In the reaction between *o*-methylthio-β-phenylethyl alcohol and hydrobromic acid the cyclic sulphonium bromide is produced just as had been found with other δ-hydroxy-sulphides in earlier experiments. The corresponding chloride was prepared by heating *o-methylthio-β-phenylethyl chloride* in solution and was characterised as the *dihydrothionaphthenmethylsulphonium chloroplatinate.*

The question arises as to how the cyclic salt is formed in the reaction with hydrobromic acid. A direct formation of the sulphonium base, which would then react with the acid, is excluded, since the hydroxy-sulphide remains neutral and unchanged even after long heating at 100° in solution. In an earlier paper (Bennett and Mosses, J., 1930, 2364) it was shown, in a similar case, that the open-chain bromo-sulphide was present in the reaction product and the cyclic sulphonium salt was regarded as formed from this by internal self-addition. But in view of the fact that the addition of an alkyl halide to a sulphide is always a reversible reaction it is apparent that the presence of the open-chain bromo-sulphide in the product is not conclusive evidence of the course of the reaction. In the present instance there are thus two possibilities, A and B, in which the bromo-sulphide is formed directly and indirectly respectively :

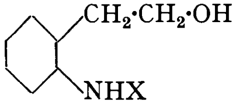

(A.)


(B.)

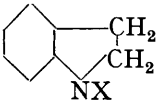
A simple test is, however, available and has been applied to decide between these alternatives. If hydrochloric acid be used in place of hydrobromic acid, the process must be much slower at each stage according to scheme A, for alcohols react far more rapidly with hydrobromic than with hydrochloric acid and alkyl bromides undergo addition to sulphides much faster than do alkyl chlorides. If the process is represented correctly by B, however, the essential reaction is between the hydroxy-sulphide and hydrogen ions and if the hydrogen-ion activity is approximately the same in equivalent solutions of hydrochloric and hydrobromic acids the rates of disappearance of acid should be approximately the same. This was found in fact to be the case and the validity of scheme B is therefore confirmed.

From the point of view developed above, a nitrogen atom should be more potent than the sulphur atom. It was therefore to be expected that an amino- or substituted amino-group in the *o*-position would exercise a strong activating influence upon the hydroxyl group in β-phenylethyl alcohol. Our criterion of reactivity, the speed of reaction with hydrobromic acid, could, however, not be applied to a substance with a free amino-group, since this must be at once converted by salt formation into the ammonium group, which could not be expected to have any such effect. It seemed possible that an acylamido-group might retain sufficient chemical activity to display the effect, although no longer strongly basic; but it was found that both the acetamido- and the benzamido-group gave evidence of hydrolysis under the experimental conditions used, and the benzenesulphonamido-alcohol was the only one tested which was sufficiently resistant to acid hydrolysis to permit accurate measurement of reaction velocity. In view of the fact that benzenesulphonic acid is a strong acid it is not surprising that the resulting figures give no evidence of special reactivity in the *o*-isomeride.

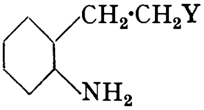
An abnormally high reactivity in the hydroxyl group of *o*-amino-β-phenylethyl alcohol (I, X = H) must, nevertheless, be responsible for the ready conversion of this substance, by shaking with arylsulphonyl chlorides and cold aqueous alkali, into the corresponding arylsulphonylindoline (II, X = SO_2Ar). The *p*-isomeride showed no such action. The nature of this unexpected reaction presented an interesting problem, which was closely studied and must be considered in detail.



(I.)



(II.)



(III.)

There appear to be at least four possible ways in which the final product might have been formed: (i) the amino-alcohol might have lost the elements of water to give the cyclic amine, which would then have been converted into the arylsulphonyl derivative; (ii) the arylsulphonamido-alcohol (I, X = SO_2Ar) might have been first formed and this converted into the cyclic product by loss of water; (iii) the arylsulphonyl chloride might have attacked the hydroxyl group, yielding the *o*-amino-β-phenylethyl arylsulphonate (III, Y = $O{\cdot}SO_2Ar$), which would then by internal self-addition give the arylsulphonic acid salt of the cyclic amine and finally the amine would be liberated and converted into its arylsulphonyl derivative; (iv) the reagents might have attacked the hydroxyl group, inserting a chlorine atom in its place, and the resulting amino-β-phenylethyl chloride (III, Y = Cl) would then have undergone ring-closure to the hydrochloride of the cyclic base and the arylsulphonyl derivative would finally have resulted.

Of these possibilities, (i) is excluded by the fact that the *o*-amino-alcohol shows no sign of conversion into the cyclic base when heated alone or with alkali but in the latter case is known to yield the corresponding styrene (Sabetay, *Bull. Soc. chim.*, 1931, **49**, 3); (ii) is disproved by the stability of the benzenesulphonamido-alcohol, which, prepared in pyridine solution, dissolves in alkali and is recovered unchanged on acidification and shows no tendency to yield the cyclic product. This possibility is also excluded by the observation that the action of not more than one molecular proportion of arylsulphonyl chloride upon the amino-alcohol produces free indoline (compare Bennett and Hafez, this vol., p. 287).

In view of the high reactivity of alkyl *p*-toluenesulphonates, the scheme (iii) is at first sight a plausible explanation. But such esters are easily hydrolysed and are unlikely to be formed directly in alkaline solution. A test on the parent β-phenylethyl alcohol showed, in fact, that the alcohol could be recovered unchanged under these conditions and no evidence was obtained of a sulphonic ester being produced. Moreover the type of reactivity possessed by the hydroxyl group in these compounds, while promoting the substitution of bromine for hydroxyl, is not such as to facilitate the formation of an acid ester (compare Bennett and Reynolds, *loc. cit.*) but rather to make this difficult. Furthermore, if the arylsulphonyl radical were introduced, one might expect it to enter the amino-group in preference to the hydroxyl group.

It thus appears that scheme (iv) is the only one of those considered which fits the facts. The amino-β-phenylethyl chloride, thus regarded as an intermediate, was not detected. The *o*-acetamido- and -benzamido-β-phenylethyl alcohols were also found to react readily in the same way with benzenesulphonyl chloride and alkali to yield *N*-acetyl- and *N*-benzoyl-indoline, thus demonstrating the activating effects of these acylamido-groups on hydroxyl.

The corresponding reaction with *o*-benzenesulphonamido-β-phenylethyl alcohol is slow and incomplete, consistently with the reduced action of the group owing to the strength of the sulphonic acid.

In the reaction of the acylamidophenylethyl alcohols with benzenesulphonyl chloride the corresponding chlorides were again not detected, but these substances were separately prepared and found to yield the acylindolines very readily by reaction with alkali.

The conversion of these substituted alcohols into chlorides by the arylsulphonyl chloride would not be without analogy. At first sight the reaction resembles most closely that discovered by Ullmann and Nadai (*Ber.*, 1908, **41**, 1870; also Ullmann and Bruck, *ibid.*, p. 3932) by which di- and tri-nitrophenols yield the corresponding chloronitrobenzenes by heating with *p*-toluenesulphonyl chloride and a tertiary base. The properties of the hydroxyl group in these compounds are acidic, however, and the reaction is more ready with the trinitro- than the dinitro-phenol, whereas the hydroxyl group of *o*-amino-β-phenylethyl alcohol has properties of a basic type resembling those of tertiary butyl alcohol or the ψ-bases of the quinoline series. It is, in fact, known that *tert.*-butyl alcohol reacts with acetyl chloride and with oxalyl chloride to give *tert.*-butyl chloride (Henry, *Compt. rend.*, 1906, **142**, 129; Adams and Weeks, *J. Amer. Chem. Soc.*, 1916, **38**, 2518) and we have ourselves found that *tert.*-butyl alcohol, heated with pyridine and *p*-toluenesulphonyl chloride at 100°, yields *tert.*-butyl chloride. The displacement of hydroxyl groups of types differing as do those of *tert.*-butyl alcohol and picric acid no doubt proceeds by different mechanisms just as the hydrolysis of the corresponding chlorides presumably does, but there can be no doubt that a high reactivity closely resembling that of *tert.*-butyl alcohol or a ψ-base is shown by *o*-amino-β-phenylethyl alcohol.

As regards the mechanism of the formation of the nitrogen ring from *o*-amino-β-phenylethyl alcohol the similarity of the change to that of *o*-methylthio-β-phenylethyl alcohol to the cyclic sulphonium salt naturally suggests the possibility of some similar direct reaction. In this case we are unable to represent such a process rationally, but we recognise that the possibility in question has not been completely excluded.

EXPERIMENTAL.

Amino-β-phenylethyl Alcohols and Derivatives.—*o*-Amino-β-phenylethyl alcohol was prepared as described by Bennett and Hafez (*loc. cit.*), where the *N*-acetyl and the *N*-benzoyl derivative are also described.

p-Amino-β-phenylethyl alcohol, made from the nitro-alcohol by reduction with iron and a little hydrochloric acid in alcoholic solution, had m. p. 107°, and its hydrochloride m. p. 163° (Pistschimuka gives m. p. 171° for the base, but this is incorrect and possibly referred to the hydrochloride). The N-*acetyl* derivative has m. p. 105° (Found: C, 67·2; H, 7·2; N, 8·0. $C_{10}H_{13}O_2N$ requires C, 66·9; H, 7·3; N, 7·8%). The N-*benzoyl* derivative forms minute elongated plates with a straight extinction, m. p. 139—140° (Found: C, 74·6; H, 5·9; N, 5·9. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2; N, 5·8%).

Arylsulphonamido-β-phenylethyl alcohols were obtained in good yield by action of the required sulphonyl chloride on the amino-alcohol dissolved in pyridine (5 mols.), the mixture being warmed for ½ hour. The products from the isomeric amino-alcohols were each soluble in alkali and reprecipitated by acid.

o-*Benzenesulphonamido-β-phenylethyl alcohol* forms small orthorhombic prisms from benzene or benzene–paraffin which have a high double refraction and a straight extinction, m. p. 89° (Found: C, 60·9; H, 5·5; N, 5·4. $C_{14}H_{15}O_3NS$ requires C, 60·6; H, 5·4; N, 5·1%). The p-*benzenesulphonamido-β-phenylethyl alcohol* forms colourless prisms with an oblique extinction, m. p. 93° (Found: C, 60·9; H, 5·3; N, 5·4%).

o- *and* p-*Iodo-β-phenylethyl Alcohols.*—These substances were prepared from the pure amino-alcohols by adding concentrated potassium iodide solution to their diazotised solutions. After warming to complete the reaction the product was distilled in steam. The o-*compound* was collected from the product of slower distillation after the dihydrobenzofuran had quickly distilled. The distillate was saturated with salt and extracted with ether, and the extract dried over sodium sulphate and distilled as a colourless oil of pleasant odour, b. p. 136°/4 mm., $d_{4°}^{25°}$ 1·7371, $n_D^{25°}$ 1·6154, $[R_L]_D$ 49·84 (calc., 49·79) (Found: C, 39·0; H, 3·7. C_8H_9OI requires C, 38·7; H, 3·6%).

The *p*-isomeride forms white crystals, m. p. 48—49° (compare Baddeley and Bennett, J., 1935, 1820) (Found: C, 39·0; H, 3·7%).

p-*Methylthio-β-phenylethyl Alcohol and Derivatives.*—*p*-Amino-β-phenylethyl alcohol (24 g.) diazotised at 5° (45 c.c. of concentrated hydrochloric acid in 75 c.c. of water with 13·5 g. of sodium nitrite) was gradually added to a well-stirred solution of potassium ethyl xanthate (45 g. in 80 c.c. of water) at 65—70°. When the mixture had cooled, the xanthic ester was removed in ether, and the extract washed twice with dilute sodium hydroxide solution and with water and evaporated. The crude ester was at once hydrolysed by heating with potassium hydroxide (25 g. in 10 c.c. of water and 40 c.c. of alcohol) for 1 hour, after which the solution remained almost clear on dilution. Methyl sulphate (15 c.c.) was now added with vigorous shaking, and the reaction completed by heating for 2 hours. After being left over-night, the oily product was extracted with ether, and the solution dried with potassium carbonate and distilled. After a small amount of distillate of b. p. 72°/18 mm. the bulk of the product boiled at 175°/18 mm., solidified in the receiver, and was the desired p-*methylthio*-β-*phenylethyl alcohol*, which crystallised in small, doubly refracting plates, m. p. 37°, from carbon disulphide or petroleum (Found : C, 64·1; H, 7·1; S, 19·3. $C_9H_{12}OS$ requires C, 64·3; H, 7·1; S, 19·0%).

This sulphide (5 g.) was oxidised with hydrogen peroxide (12 c.c. of 90 vol.) in glacial acetic acid (30 c.c.) on the water-bath for 2 hours. After most of the acetic acid had been distilled, and the remainder had been warmed with aqueous sodium hydroxide to hydrolyse any acetyl derivative, the alkali was neutralised and the solution evaporated. The p-*methylsulphonyl*-β-*phenylethyl alcohol* was extracted in benzene, from which it crystallised in doubly refracting needles with a straight extinction, m. p. 64° (Found : C, 54·4; H, 5·7. $C_9H_{12}O_3S$ requires C, 54·0; H, 6·0%).

To the *p*-methylthiophenylethyl alcohol (5 g. in 40 c.c. of chloroform) were successively added dimethylaniline (7·5 c.c.) and thionyl chloride (7 c.c. in 10 c.c. of chloroform), the mixture, after 2 hours, being heated for ¼ hour and poured into dilute acid and well washed. p-*Methylthio*-β-*phenylethyl chloride* was thus obtained as an almost colourless oil, b. p. 131°/4 mm. (Found : C, 58·2; H, 6·2; Cl, 18·6. $C_9H_{11}ClS$ requires C, 57·9; H, 5·9; Cl, 19·0%).

o-*Methylthio*-β-*phenylethyl Alcohol and Derivatives*.—*o*-Amino-β-phenylethyl alcohol (24 g.) was diazotised (45 c.c. of concentrated hydrochloric acid with 135 c.c. of water and 13·5 g. of sodium nitrite) and converted into the xanthic ester as for the *p*-isomeride. Alcoholic potassium hydroxide was added to this ester and, after the mixture had cooled, the alcohol was distilled quickly in a current of nitrogen. The solution was diluted and extracted once with ether to remove alkali-insoluble materials, and methyl sulphate (12 c.c.) at once added. The product was isolated as for the *p*-isomeride and obtained as an oil, b. p. 169°/16·5 mm. (yield, 35% of the amine used). In order to secure a high degree of purity for the purpose of the reaction velocity measurements this substance was regenerated from the nitro- or dinitro-benzoate. The p-*nitrobenzoyl* derivative formed pale yellow needles with a straight extinction, m. p. 66—67°, from paraffin (b. p. 60—80°) (Found : N, 4·5; S, 10·4. $C_{16}H_{15}O_4NS$ requires N, 4·4; S, 10·1%). Carbon analyses tended to be high (Found : C, 61·4; H, 4·7. Calc. : C, 60·6; H, 4·7%). The 3 : 5-*dinitrobenzoyl* derivative formed bright yellow prisms with a straight extinction, m. p. 93°, from paraffin (b. p. 80—100°) (Found: N, 7·8. $C_{16}H_{14}O_6N_2S$ requires N, 7·7%). Carbon analyses were again high (Found : C, 53·9; H, 3·8. Calc. : C, 52·9; H, 3·9%).

The pure o-*methylthio*-β-*phenylethyl alcohol* was prepared by hydrolysing the repeatedly crystallised dinitrobenzoyl derivative and was thus obtained as a straw-coloured oil of faint pleasant odour, b. p. 165°/12·5 mm., 293°/766 mm. (uncorr.) without decomposition (Found : C, 64·2; H, 7·2; S, 18·8. $C_9H_{12}OS$ requires C, 64·3; H, 7·1; S, 19·0%). It had $d_{4^\circ}^{25^\circ}$ 1·12521 and $n_{\mathrm{D}}^{25^\circ}$ 1·5874, whence $[R_L]_{\mathrm{D}}$ 50·25. The value calculated from the atomic constants of Eisenlöhr and of Price and Twiss is 49·72. The difference of half a unit between these two figures is, however, normal for substances with a sulphur atom attached to the aromatic nucleus, as was found in a series of such compounds a few years ago (Bennett, Heathcoat, and Mosses, J., 1929, 2569) where an exaltation of 0·3—0·8 unit was always observed. A similar exaltation is shown, too, by the data in the literature for phenyl methyl sulphide ($[R_L]_{\mathrm{D}}$ 39·37. Calc., 39·00).

This sulphide was oxidised with hydrogen peroxide in glacial acetic acid, as for the *p*-isomeride, and yielded the o-*methylsulphonyl*-β-*phenylethyl alcohol* as an oil, b. p. 210°/3·5 mm. (Found : C, 54·4; H, 5·7. $C_9H_{12}O_3S$ requires C, 54·0; H, 6·0%).

Thionyl chloride and dimethylaniline acted on the parent alcohol to produce o-*methylthio*-β-*phenylethyl chloride*, a nearly colourless oil, b. p. 122°/4 mm. (Found : C, 58·3; H, 5·6; Cl, 18·8. $C_9H_{11}ClS$ requires C, 57·9; H, 5·9; Cl, 19·0%). Heated at 100° in phenol solution for several hours, this substance yielded a cyclic sulphonium salt. The phenol was removed in steam, the residual solution extracted repeatedly with ether to remove unchanged material, and the product then precipitated with chloroplatinic acid. *Dihydrothionaphthenmethylsulphonium chloroplatinate* was thus obtained as a yellow crystalline powder, m. p. 100° (decomp.) (Found : Pt, 27·1. $C_{18}H_{22}Cl_6S_2Pt$ requires Pt, 27·5%).

Preparation of o- *and* p-*Methoxy*-β-*phenylethyl Alcohols*.—(i) *o*-Amino-β-phenylethyl alcohol (21 g.) was diazotised in hydrochloric acid solution (15 c.c. of concentrated acid in 60 c.c. of water with 11 g. of sodium nitrite) and warmed until evolution of gas ceased. A concentrated solution of sodium hydroxide (22 g.) was added, and a little dihydrobenzofuran removed in a current of steam. The solution was then nearly neutralised with dilute sulphuric acid, and carbon dioxide passed to liberate the phenol. The solution was saturated with sodium chloride, and the product extracted with ether, dried over sodium sulphate, and distilled. *o*-Hydroxyphenylethyl alcohol was thus obtained (yield, 70%), b. p. 150°/3 mm. (Stoermer and Kahlert, *Ber.*, 1901, **34**, 1806, give b. p. 168—169°/12 mm. for this substance, obtained as one of the products of the action of alcoholic potash on coumarone). Methylation with 10% sodium hydroxide solution and methyl sulphate gave o-*methoxy*-β-*phenylethyl alcohol* as an oil, b. p. 123°/5 mm. (Found: C, 70·7; H, 8·2. $C_9H_{12}O_2$ requires C, 71·0; H, 7·9%). It had $d_{4°}^{25°}$ 1·0939, $n_D^{25°}$ 1·5340, whence $[R_L]_D$ 43·17 (calc., 43·25).

(ii) p-*Methoxy*-β-*phenylethyl alcohol* was obtained similarly by methylating the phenol prepared from the *p*-aminophenylethyl alcohol as for the *o*-isomeride. It was also obtained direct in the following way: To *p*-aminophenylethyl alcohol (20 g.), dissolved in methyl alcohol (200 c.c.) with concentrated sulphuric acid (16 c.c.), a solution of sodium nitrite (11·5 g. in 25 c.c. of water) was slowly added at 5—10°. The solution was warmed slowly to 50° and then kept at 60° until gas evolution ceased. The inorganic salts were removed by filtration, and the free acid neutralised with dilute potassium hydroxide solution. Alcohol was distilled, and the product extracted with ether. The solution was washed with dilute aqueous sodium hydroxide, with dilute acid and with water, and dried over sodium sulphate. Distillation yielded a colourless oil, b. p. 148—149°/19 mm., solidifying in the receiver, which was crystallised from light petroleum. It had m. p. 27·5—28° (Found: C, 71·2; H, 7·7. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%). (Yield, direct from the amine, 30% of the calculated. Better yields were obtained by conversion into the phenol and methylation of this as with the *o*-isomeride.)

Measurements of Velocity of Reaction with Hydrobromic Acid.—The methods used were as described in previous papers (Bennett and Mosses, Bennett and Reynolds, *locc. cit.*), reaction mixtures being used with initial concentrations approximately in the molecular ratio alcohol : acid : water = 1 : 2 : 10. With those alcohols which reacted but slowly at 80° a quantity of the reaction mixture was made up at laboratory temperature and aliquot portions were measured out into a series of tubes, which were then sealed and heated in the thermostat at 80·0° ± 0·05°. With more reactive alcohols the contents of each tube were separately measured or weighed into the tube, cooled in ice, and the tube sealed and finally transferred with shaking to the thermostat.

Bromophenol-blue or methyl-red was used as indicator in the titrations. Where the reaction was rapid, it was followed as far as possible towards the point of equilibrium, and the equation for a reversible reaction applied (Bennett and Mosses, *loc. cit.*). When it was slow, it was not practicable to follow the reaction so far and the simple equation for a reaction of second order was used.

The data for two substances are given in detail, the symbols having the same meaning as before.

β-Phenylethyl alcohol at 80·0°. $a = 0·4837$ mol./l., $b = 1·122$, $d = 6·153$, $K = 9·97$.

t (mins.)	60	120	180	300	360	480	600	720
0·1223N-NaOH, c.c.	17·41	17·16	16·90	16·49	16·25	15·97	15·73	15·33
$k_1 \times 10^4$	—	5·65	6·00	5·80	6·10	5·80	6·15	—

Mean 5·90 × 10^{-4}.

p-*Methylthio-β-phenylethyl alcohol at* 80·0°. $a = 0·5705$ mol./l., $b = 1·095$, $d = 6·008$, $K = 12·68$.

t (mins.)	65	20	180	240	300	420	480	600	780
0·1223N-NaOH, c.c.	16·66	16·44	15·70	15·32	14·92	14·42	14·16	13·75	13·41
$k_1 \times 10^3$	—	1·09	1·14	1·14	1·15	1·08	1·09	1·09	—

Mean 1·10 × 10^{-3}.

The mean values of k for the whole series have been given in the table on p. 653 (time in minutes, concentrations in mols./l.). These represent figures for k_1, the velocity of the forward reaction in general, but for the nitro- and iodo-alcohols they are the ordinary second-order coefficients. The observed mean values at two temperatures for the isomeric methylthio-β-phenylethyl alcohols are: *ortho* at 30°, $k_1 = 4·43 \times 10^{-3}$; at 40°, $14·1 \times 10^{-3}$, whence the activation energy is 21,800 cals. and the velocity at 80° is $k_1 = 0·684$: *para* at 80°, $k_1 = 1·10 \times 10^{-3}$; at 90°, $2·62 \times 10^{-3}$, whence the activation energy is 22,100 cals.

Comparison of Rates of Reaction of o-*Methylthio*-β-*phenylethyl Alcohol with Hydrochloric and Hydrobromic Acids.*—Comparative tests were made over equal intervals of time with pairs of solutions of the alcohol in phenol with hydrochloric and hydrobromic acids, the concentrations being equivalent in the parallel experiments and the acid and alcohol being present in the molecular ratio of 2 : 1 in each case.

		Extent of reaction in % of total possible.	
Time, mins.	Temp.	With HCl.	With HBr.
30	30°	3·6	3·3
60	41·5	19·0	18·6
63	46	23·0	21·0

Experiments showing Special Reactivity in o-*Amino-β-phenylethyl Alcohol and its Derivatives.*—(1) When *o*-amino-β-phenylethyl alcohol was shaken with *p*-toluenesulphonyl chloride (slightly more than 1 mol.) and 10% aqueous sodium hydroxide in order to prepare the arylsulphonyl derivative of this amine, the only solid product was a little *p*-toluenesulphonylindoline, m. p. 100°, insoluble in alkali. The mother-liquor smelt strongly of a base and when more toluenesulphonyl chloride was added it yielded further quantities of the same substance.

Similar results were obtained with benzenesulphonyl chloride, the product being benzenesulphonylindoline, m. p. 133°.

(2) In either case, by using exactly one molecular proportion of the acid chloride, the cyclic amine was produced and could be removed in steam and isolated (compare Bennett and Hafez, *loc. cit.*).

(3) When acetyl chloride or benzoyl chloride was used in place of the arylsulphonyl chlorides, no cyclic product was formed.

(4) Equivalent amounts of phenylethyl alcohol and benzenesulphonyl chloride were shaken with 10% alkali solution under similar conditions. The oil recovered had the smell and properties of unchanged phenylethyl alcohol and yielded with phenyl *iso*cyanate the phenylurethane, m. p. 80° (Found : C, 74·5; H, 6·0; N, 6·1. Calc. : C, 74·6; H, 6·2; N, 5·8%).

(5) *o*-Benzamido-β-phenylethyl alcohol (1 g. in 15 c.c. of acetone) was mixed with 10% sodium hydroxide solution (9 c.c.), benzenesulphonyl chloride (9·8 c.c.) added gradually, and the whole shaken for ½ hour. The acetone was evaporated on the water-bath; the oil which then separated solidified on cooling and proved to be *N*-benzoylindoline, m. p. 118° after crystallisation from spirit (Found : C, 81·0; H, 5·5; N, 5·8. Calc. : C, 80·7; H, 5·8; N, 6·3%). *o*-Acetamido-β-phenylethyl alcohol, similarly treated, yielded *N*-acetylindoline, m. p. 105° (Found : C, 74·3; H, 6·8; N, 8·8. Calc. : C, 74·5; H, 6·8; N, 8·7%).

When *o*-benzenesulphonamidophenylethyl alcohol was subjected to the same treatment, a small amount of impure benzenesulphonylindoline was formed. The crude material had m. p. 115°, but a mixture with pure benzenesulphonylindoline melted at 131°. The bulk of the *o*-benzenesulphonamido-alcohol was recovered unchanged by acidifying the alkaline mother-liquor.

(6) To *o*-benzamido-β-phenylethyl alcohol (2 g.), dissolved in chloroform (30 c.c.) with dimethylaniline (2 c.c.), thionyl chloride (2 c.c. in 10 c.c. of chloroform) was gradually added, and the mixture kept for several hours. The solution was then washed thrice with concentrated hydrochloric acid and repeatedly with water, dried over calcium chloride, and evaporated. The residual oil solidified when stirred with a little water, crystallised from aqueous alcohol in doubly refracting plates with a straight extinction, m. p. 119·5°, and was o-*benzamido-β-phenylethyl chloride* (Found : C, 69·5; H, 5·3; N, 5·2; Cl, 13·3. $C_{15}H_{14}ONCl$ requires C, 69·4; H, 5·4; N, 5·4; Cl, 13·6%). This substance was dissolved in acetone, and an excess of sodium hydroxide added. The temperature rose and after a few minutes the material was recovered by evaporating the acetone. It contained no chlorine, had m. p. 118°, and proved to be *N*-benzoylindoline (mixed m. p.).

(7) To *o*-amino-β-phenylethyl chloride hydrochloride (Bennett and Hafez, *loc. cit.*) (1·2 g.), dissolved in dry pyridine (3 c.c.), acetyl chloride (2 c.c.) was added slowly. After a few minutes, water was added, and the solid product collected and washed well with hydrochloric acid and water. o-*Acetamido-β-phenylethyl chloride*, so obtained, crystallised from 75% alcohol in needles with an oblique extinction, m. p. 120° (Found : C, 60·6; H, 6·2; N, 7·4; Cl, 18·1. $C_{10}H_{12}ONCl$ requires C, 60·8; H, 6·1; N, 7·1; Cl, 18·0%). This substance was at once converted by the action of alkali in acetone into *N*-acetylindoline, m. p. and mixed m. p. 105°.

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