

An electronic formula, based upon these determinations, has been proposed.

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[CONTRIBUTION FROM EAST LONDON COLLEGE, UNIVERSITY OF LONDON]

THE PINACOL-PINACOLONE REARRANGEMENT. THE EXAMINATION OF SOME ORTHO-SUBSTITUTED BENZOPINACOLS

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It is generally recognized that the values for the relative migratory powers of aromatic hydrocarbon radicals in the pinacol-pinacolone rearrangement are least liable to error when they are obtained from studies of the rearrangement of tetraarylpinacols, for the reason that in such cases there is the least possibility of the end products of the reaction arising in any other way than by a direct pinacol-pinacolone change. In this connection *o*-substituted benzopinacols have been but little examined; of the simple compounds of this class only *sym*.-2,2'-dichlorobenzopinacol and *sym*.-2,2'-dibromobenzopinacol have been at all fully investigated.¹ These pinacols rearranged slowly and the resulting pinacolones were very resistant to attack by alcoholic potash so that a complete decomposition thereby into the corresponding triarylmethanes and aromatic acids was not effected, but it was concluded that in the rearrangements only the unsubstituted phenyl group underwent migration.

Recently Bailar² stated that *sym*.-2,2'-dimethylbenzopinacol and *sym*.-2,2'-dimethoxybenzopinacol could not be rearranged either by iodine and acetic acid, or by acetyl chloride and acetic acid, prolonged treatment with the latter reagent giving rise to unidentifiable oils. He considered these results to be in good agreement with the theoretical conclusions of Lagrave.³ Bailar overlooked the fact that the rearrangement of *sym*.-2,2'-dimethylbenzopinacol had already been described⁴ and that of the phenyl and *o*-tolyl groups the former had been shown to migrate the more readily.⁵

We therefore decided to repeat the rearrangement of *sym*.-2,2'-dimethylbenzopinacol (I), determining the relative migratory powers of the phenyl

¹ Koopal, *Rec. trav. chim.*, **34**, 115 (1915).

² Bailar, *THIS JOURNAL*, **52**, 3596 (1930).

³ Lagrave, *Ann. chim.*, **10**, VIII, 363 (1927).

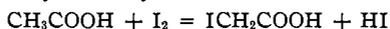
⁴ Hatt, *J. Chem. Soc.*, 1623 (1929).

⁵ Of the ten pinacols described by Bailar as new, two were already known: *sym*.-2,2'-dimethylbenzopinacol [W. D. Cohen, *Rec. trav. chim.*, **38**, 123 (1919); Boyd and Hatt, *J. Chem. Soc.*, 898 (1927)] and *sym*.-2,2'-dimethoxybenzopinacol [Cohen, *Rec. trav. chim.*, **38**, 123 (1919), and **39**, 258 (1920)].

and *o*-tolyl radicals, and also to examine *sym*.-2,2'-dimethoxybenzopinacol (II).

The Rearrangement of the Pinacols and Evidence for Their Free Radical Dissociation in Acetic Acid Solution.—The rearrangement of these pinacols with a solution of iodine in acetic acid proceeds readily, but a successful rearrangement with acetyl chloride has not been effected. The transformations with the first reagent must be practically complete, for with both pinacols 90% yields of the pinacolones were isolated. A further test was possible in the case of pinacol (II) which gives a strong green-black solution in sulfuric acid,⁶ whereas the resulting pinacolones give only pale yellow-brown solutions. By means of this sensitive test it was shown that no pinacol remained after one hour's refluxing with iodine and acetic acid. Pinacol (I) rearranges at a slower rate than (II) and to be complete the treatment must be continued for eight to twelve hours according to the amount of iodine employed.

Some observations made in connection with this problem throw light upon the nature of the rearranging agent. At its boiling point a solution of iodine in acetic acid attacks the methoxyl groups of pinacol (II). For example, with a rearrangement carried out in the usual Zeisel apparatus for the estimation of methoxyl, the amount of silver iodide collected was equivalent to 1.8% of the methoxyl radicals present in the pinacol. The production of methyl iodide was attributed to the presence of hydriodic acid, which may possibly arise by a reaction such as the following⁷



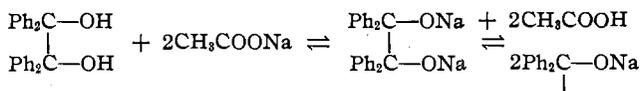
In our experiment, if the iodine had reacted completely in this way, the hydriodic acid could have attacked 1.7% of the pinacol. If sodium acetate was added to the iodine and acetic acid, the reagent was unable to effect rearrangement and the small amount of iodine present was rapidly removed. Failure to rearrange is, nevertheless, not due to lack of iodine, for no rearrangement took place when iodine was added to the solution at a rate which maintained the concentration at a value sufficient in absence of sodium acetate to effect rearrangement.

In further experiments using benzopinacol it was found that sodium acetate and iodine react alone at an appreciable rate, but in presence of the pinacol the iodine disappears more rapidly. Using sufficient iodine the pinacol is converted almost quantitatively to benzophenone. If the iodine does not suffice to convert the pinacol to the ketone, then, as the iodine is used up, the solution becomes first colorless and then rapidly acquires a distinct violet to blue color, which is the more pronounced the greater the concentration of sodium acetate. Subsequent addition of iodine reverses these color changes, and with suitable additions of iodine these variations

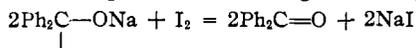
⁶ Compare Wizinger and Fontaine, *Ber.*, **60**, 1377 (1927).

⁷ Lapworth, *J. Chem. Soc.*, **85**, 41 (1904); Shaw, *ibid.*, **123**, 2233 (1923).

in color may be obtained several times. Such phenomena suggest that the benzopinacol is partially transformed into free radicals of the metal-ketyl type and of these sodiobenzophenone appears the most likely to arise, being produced in small quantities according to the equation



sodium acetate in acetic acid thus simulating the behavior of sodium ethoxide in ethyl alcohol⁸ and of potassamide in liquid ammonia.⁹ The reaction with iodine would then proceed according to the equation of Schlenk¹⁰



Support for this view is found in the observation that a stream of dry air led through a solution of benzopinacol and sodium acetate in acetic acid oxidizes the pinacol to benzophenone. However, it is necessary to indicate two observations that are not quite in agreement with this view: the first, that we have failed to observe the development of a blue color in a solution of benzopinacol and sodium acetate in acetic acid before the addition of any iodine; the second, that a current of dry air is able to convert benzopinacol in boiling acetic acid into benzophenone. Alternatively, this last observation and those concerning solutions of the pinacol in acetic acid and sodium acetate could be explained by supposing partial dissociation of the pinacol into diphenylhydroxymethyl.

Experiments have shown that benzopinacol is rearranged more slowly in an acetic acid solution of iodine than by a similar equimolecular solution of hydriodic acid (containing but a slight trace of iodine). In the first solution it is possible to observe the complete disappearance of the color due to iodine and to find that the rearrangement is nevertheless complete. Since previous experiments have shown that such solutions always contain hydriodic acid, this latter would seem to be the effectual agent in such rearrangements. Whether the presence of a little iodine has a promoting influence cannot be stated; what appears more important is the hydrogen concentration, any great decrease in the value of which, by the addition of sodium acetate, suppresses rearrangement.

Experimental

The Preparation of *Sym.*-2,2'-dimethoxybenzopinacol.—2-Methoxybenzophenone was reduced to the pinacol using zinc dust and acetic acid by the method already described for 2-chlorobenzophenone.¹¹ Reduction for five days at 25° gave much the better yield. The pinacol so obtained melted at 165–168° and under the microscope

⁸ Schlenk and Thal, *Ber.*, **46**, 2840 (1913).

⁹ Wooster, *THIS JOURNAL*, **50**, 1388 (1928).

¹⁰ Schlenk, *Ber.*, **44**, 1182 (1911).

¹¹ Hatt, *J. Chem. Soc.*, 1629 (1929).

was seen to consist of two types of crystals: long rectangular prisms (I) and rhombic plates (II), separable by fractional crystallization from chloroform and alcohol, the former being the less soluble. Tetraarylpinacols melt with decomposition,¹² and the melting point depends upon the rate of heating. In the present two cases the melting points lie too close together to provide a method for distinguishing the pinacols. Under comparable conditions (I) melted at 173–175° and (II) at 174–176°. Either is completely liquid after heating for twenty-five minutes at 154°.

Anal. Calcd. for $C_{28}H_{26}O_4$: C, 78.83; H, 6.15. (I) Found: C, 78.72; H, 6.19. (II) Found: C, 78.75; H, 6.19.

Rearrangement of Sym.-2,2'-dimethoxybenzopinacol.—The pinacol (1.93 g.), refluxed for four hours with dry glacial acetic acid (20 cc.) and iodine (0.04 g.) and poured into 50 cc. of water containing a little sodium sulfite, gave a white crystalline precipitate, which, after filtering, washing with water, and drying at 100°, melted at 157–158° and weighed 1.7 g. (92% of theoretical). Four recrystallizations, each time employing a different solvent, raised the melting point to 161°.

Anal. Calcd. for $C_{28}H_{26}O_3$: C, 82.33; H, 5.93; mol. wt., 408. Found: C, 82.43; H, 6.15; mol. wt., 405 (in camphor).

Nevertheless, this was still a mixture of the two possible pinacolones, for rupture with alcoholic potash produced a mixture of *o*-anisic acid and benzoic acid. A second rearrangement in which the time of refluxing was one hour gave precisely the same product in 92% yield.

The Action of Alcoholic Potash on the Pinacolones.—As mentioned, Koopal was unable to transform di-ortho-substituted benzopinacolones completely into the corresponding triarylmethanes and aromatic acids. We have experienced the same difficulty when using the crude pinacolones for the estimation of the migratory powers of groups, although one of us¹¹ found that pure *o*-toluyl-*o*-tolylidiphenylmethane could be transformed almost quantitatively into the methane and acid. Bailar observed that occasionally with meta- or para-substituted benzopinacolones the alcoholic potash solutions became a deep brown color. He found that the values for the migratory powers obtained from such experiments were never concordant and rejected them. In all of our experiments a brown color and finally a brown precipitate were produced. For ortho substituted pinacols we believe the formation of this brown precipitate to be due to the comparatively slow rearrangement of the pinacol permitting of the simultaneous formation of the hydrol and ketone by thermal decomposition, and of the ketone by oxidation, if air is not excluded. The ketone so contaminating the pinacolone is then reduced by the alcoholic potash to the hydrol and the acetaldehyde produced resinifies.¹³ Thus, if benzopinacolone, resulting from the treatment of the pinacol with iodine and acetic acid, is treated, without preliminary crystallization, with alcoholic potash, the solution does not become brown after prolonged boiling. But the brown precipitate is produced if a little benzopinacol is added to the solution, or by prolonged refluxing of the acetic acid solution of the pinacol before rearrangement. The low yields of acids we obtained (not more than 60% of the theoretical) appear to be connected with this phenomenon rather than due to incomplete fission of the pinacolones. In one case where 1.74 g. of the methoxylated pinacolone gave 0.274 g. of acids by refluxing for one hundred hours with alcoholic potash, a further like treatment of the neutral products yielded only an additional 0.016 g. Because, although the yields of acids varied considerably, their composition remained constant, we consider that the migratory powers calculated on this basis are essentially correct and have a maximum error of about 5%.

¹² Thörner and Zincke, *Ber.*, 10, 1473 (1877).

¹³ Compare Montagne, *Rec. trav. chim.*, 27, 327 (1908); 31, 298 (1912).

Determination of Migratory Powers.—The pinacol (2 g.) was converted to the pinacolone as already described, the latter dried, transferred to an all-glass apparatus and there refluxed for one hundred hours with a solution of potassium hydroxide (5 g.) in absolute alcohol (50 cc.). This solution was poured into 300 cc. of water and the liquors evaporated three times to two-thirds of their bulk to remove the alcohol completely. The insoluble material was extracted with chloroform or benzene, the aqueous liquors acidified and extracted with one of the above solvents and these last extracts dried, evaporated, and the acids dried to constant weight at room temperature.

The equivalent weight of the mixed acids was determined by one or more of the following methods. (I) The methoxy content was determined by the usual Zeisel method. To obtain reliable results it was necessary to remove all foreign ethoxyl containing substances, which was accomplished by repeated evaporation of the alkaline liquors and the use of chloroform or benzene as extractant as described above. (II) By titration with standard baryta solution. (III) The salicylic and benzoic acids generated in method (I), after decolorization in aqueous solution with sulfurous acid, were extracted in benzene, the solution washed with water, evaporated and the salicylic acid estimated according to the method of Bougeault.¹⁴ After removing the purple precipitate of "tetraiododiphenylene quinone," benzoic acid was extracted from the aqueous filtrates and identified in the usual way. The yields of benzoic acid were low but agreed fairly well with the figures obtained by the above three methods.

The estimations of the equivalent weight of the mixed acids by the three methods are in good agreement. Owing to the extra manipulation, method (III) is probably the least accurate. Some of the results are set out in Table I; from them the mean values of the relative migratory powers of the phenyl and *o*-anisyl groups are found to be 1.00 and 0.30.

TABLE I

No.	Pinacol, g.	Yield of acids, g.	Percentage by weight of <i>o</i> -anisic acid in the mixed acids		
			Method (I)	Method (II)	Method (III)
1	2.018	0.274	81.0	80.9	..
2	2.002	.280	81.7	..	77
3	2.000	.327	81.6
4	1.926	.390	83.3

2-Methylbenzophenone and 2,2'-Dimethylbenzopinacol.—Several processes have been given for the preparation of 2-methylbenzophenone. We have found that 2-methylbenzohydrol can be oxidized to this ketone almost without any side chain oxidation. On the other hand, Zincke,¹⁵ Senff,¹⁶ and others found that complete oxidation of the methylene group in the benzyltoluenes could not be accomplished without considerable oxidation of the methyl group.

2-Methylbenzohydrol was readily obtained from *o*-tolylmagnesium bromide and benzaldehyde. 10 g. of the hydrol was added with vigorous stirring to a mixture of 20 g. of potassium dichromate, 16.5 cc. of concentrated sulfuric acid and 95 cc. of water. The mixture was stirred at 45–50° for half an hour and then poured into aqueous sodium hydroxide. After almost neutralizing with sulfuric acid, extraction with ether gave 9.3 g. of almost pure ketone.

Reduction of the ketone with zinc dust and acetic acid proceeded smoothly, giving the pinacol, m. p. 160–161° (from chloroform and alcohol). Heated with glacial acetic

¹⁴ Bougeault, *Compt. rend.*, **146**, 1403 (1908); *J. pharm. chim.*, [VI] **28**, 145 (1908).

¹⁵ Zincke, *Ann.*, **161**, 93 (1872).

¹⁶ Senff, *ibid.*, **220**, 237 (1883).

acid and iodine for twelve hours, the pinacol yielded the stable pinacolone.¹¹ Apart from this extra time required for the rearrangement, the relative migratory powers of the phenyl and *o*-tolyl groups were determined essentially according to the procedure for the previous case.

Ninety-seven to ninety-eight per cent. of the theoretical yields of the crude pinacolone were obtained. In three experiments the weights of acid obtained from 1.834, 1.816 and 2.000 g. of pinacol were, respectively, 0.267, 0.259 and 0.329 g. The equivalent weights determined by method (II) were 136.3, 135.1 and 138.2 (*o*-toluic acid requires 136), showing that there is almost exclusive migration of the phenyl group.

The Oxidation of Benzopinacol in Acetic Acid Solution.—(A) One gram of benzopinacol was added to a mixture of 10 cc. of pure acetic acid,¹⁷ 1 g. of iodine and 2 g. of fused sodium acetate. The mixture was refluxed for one-half hour, excluding moisture, cooled and poured into dilute sulfurous acid. The crystalline benzophenone was filtered off and dried to constant weight (0.98 g.). It melted at 45–47°; 48–49° after one crystallization. In a second experiment the crude benzophenone was refluxed with alcoholic potash and the organic acids produced were estimated as in the fission of a pinacolone; 0.008 g. of benzoic acid was produced.

(B) Two grams of benzopinacol, 2 g. of sodium acetate and 20 cc. of acetic acid were refluxed on an oil-bath in a current of dry air, freed of carbon dioxide. After five hours the products were poured into water and the insoluble matter filtered off. The aqueous liquors did not liberate iodine from potassium iodide solution and experiments showed that had sodium peroxide been produced it would have been destroyed under the conditions of the experiment. The solid product, 1.85 g., was separated with petroleum ether into benzopinacol (0.5 g.) and benzophenone (0.9 g.). The crude material gave a light orange color with sulfuric acid but no benzhydrol could be isolated. In an experiment where the air was replaced by nitrogen, 80% of the pinacol was recovered in a state of purity.

(C) The reaction was carried out as in (B) but in absence of sodium acetate. The oxidation did not proceed so smoothly; using 1.9 g. of benzopinacol there were isolated 0.9 g. of benzophenone and 0.2 g. of benzopinacol.

Conclusion

Sym.-2,2'-dimethylbenzopinacol and *sym*.-2,2'-dimethoxybenzopinacol have been rearranged. From the rearrangement of the second pinacol, a value is obtained for the migratory power of the *o*-anisyl group (0.30) which exceeds that of the *m*-anisyl group (0.20). Lagrave's generalizations are therefore incorrect, in so far as they predict, as Bailar states, the inability of these pinacols to rearrange and of all *o*-substituted groups to undergo migration.

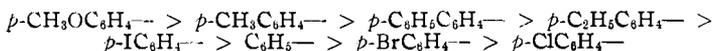
The present observations stand in agreement with the previously existing data in this field. Thus, there seems to be no case of a di-ortho-substituted benzopinacol that has failed to rearrange. And again, although the *o*-anisyl group is the first simple *o*-substituted group whose migration in the rearrangement of tetraarylpinacols has been established, some closely related groups were known to migrate. Examples of this kind occur in the rearrangement of bis-diphenylene-ethylene glycol¹⁸ and of 1,1-diphenyl-2,2-

¹⁷ Purified according to the method of Orton and Bradfield, *J. Chem. Soc.*, 125, 960 (1924).

¹⁸ Gomberg and Bachmann, *THIS JOURNAL*, 49, 236 (1927).

diphenylene-ethylene glycol,¹⁹ where in terms of the Tiffeneau-Meerwein mechanism the migration of the "ortho-linked" group is enforced. Observations have also been made pointing to the ability of similar groups to migrate where this does involve competition with the phenyl group. Elbs²⁰ found evidence for this in the case of the 2,5-dimethylphenyl group, and in the tetraarylpinacol series the α -naphthyl group appears to have a greater migratory power than the phenyl group, while its resemblance to an ortho-substituted phenyl group is well known.^{2,20,21}

The data concerning symmetrical di-ortho-substituted benzopinacols may be regarded in the following way. For the corresponding para compounds the series:

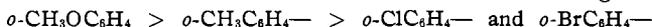


is obtained when the migrating groups are arranged in order of their decreasing migratory power. For the ortho compounds this order is modified by the superposition of an "ortho effect." This "effect" may not be entirely sterical in nature,²² but at present the data agree with the simple assumption that the essential difference between the migration of ortho and para substituted radicals is that the former is rendered much more difficult by opposition of a sterical kind. Although sterical effects cannot yet be evaluated with certainty, the earlier investigations,²³ the work of Kindler²² and the calculations from x-ray analysis,²⁴ all agree in the order of increasing sterical effect:



Moreover, that it is difficult to attach three *o*-tolyl groups to the same carbon atom by means of the Grignard reagent,¹¹ whereas, by this means, the addition of three *o*-anisyl groups takes place readily,²⁵ may be taken to indicate that sterical opposition to the *o*-tolyl group is much greater than to the *o*-anisyl group.

The formation of a series indicating the order of increasing migratory power for ortho-substituted radicals can only be obtained by the superposition of this "ortho effect" upon the series for para radicals when the exact relationship between these two quantities is known. But however this combination is to be effected, it can be seen that it may be given the order



which is in agreement with the results so far obtained



¹⁹ Meerwein, *Ann.*, **396**, 200 (1913).

²⁰ Elbs, *J. prakt. Chem.*, [II] **35**, 477 (1887).

²¹ Bachmann and Shankland, *THIS JOURNAL*, **51**, 306 (1929).

²² Compare Kindler, *Ann.*, **464**, 278 (1928).

²³ Werner, "Lehrbuch der Stereochemie." 1904, p. 377.

²⁴ Adams and Stanley, *THIS JOURNAL*, **52**, 1200 (1930).

²⁵ Baeyer and Villiger, *Ber.*, **35**, 3025 (1902).

Summary

Sym.-2,2'-dimethylbenzopinacol and *sym.*-2,2'-dimethoxybenzopinacol have been rearranged to the corresponding pinacolones and the relative migratory powers of the phenyl, *o*-tolyl and *o*-anisyl groups have been determined.

Benzopinacol is oxidized by gaseous oxygen in acetic acid solution, either with or without the addition of sodium acetate, to benzophenone. The same oxidation is accomplished much more rapidly by a solution of iodine and sodium acetate in acetic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY OF THE JOHNS HOPKINS
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CHEMICAL INVESTIGATION OF RAUWOLFIA CAFFRA. I. RAUWOLFINE

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The genus *Rauwolfia*, belonging to the natural order *Apocynaceae*, is widespread throughout the tropics and some forty-two species are known. Although most species are actively poisonous and many are reputed to possess medicinal value, information concerning their chemistry or pharmacology is extremely meager. There are occasional references in the literature wherein the investigators¹ lay claim to having obtained active crystalline bodies from some of the East Indian *Rauwolfia* but the investigations were limited in scope and the reports are vague. Accordingly, when a supply of the bark of a South African species of *Rauwolfia* became available, the present investigation was undertaken with the hope that some definite information would be forthcoming concerning the constituents of the bark responsible for the physiological activity and, furthermore, that if chemical individuals could be isolated, a study of their properties from a chemical and pharmacological viewpoint might prove of value.

The only available information concerning the South African *Rauwolfia* under investigation is contained in a report² from which the following facts are taken. An investigation was made of the nature of the active principle of the so-called "Quinine Tree" of the Transkei, the "*Umjela*" as it is known by the natives. This tree, now identified as *Rauwolfia caffra* (formerly as *Tabernaemontana ventricosa*, Hochst), grows in the Gxwaleni

¹ Wehmer, "Die Pflanzenstoffe," G. Fisher, Jena, 1931, Vol. ii, p. 981; Greschoff, *Ber.*, **23**, 3543 (1890).

² Juritz, "Report of the Senior Analyst for the Year 1901," Cape Town, 1902, p. 58.