[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Pinacol Rearrangement in the Heterocyclic Series. III. Numerical Migratory Aptitudes

BY MATTHEW R. KEGELMAN AND ELLIS V. BROWN

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Symmetrical analogs of benzopinacol containing two 4-methoxyphenyl groups with either two 2-thienyl groups or two 2-furyl groups have been synthesized, as has another such analog containing two 2-thienyl groups with two 2-furyl groups. The rearrangement of the first pinacol showed that the migratory aptitude of the 2-thienyl group is 1,000 while those of the second and third pinacols indicated that the migratory aptitude of the 2-furyl group is much larger.

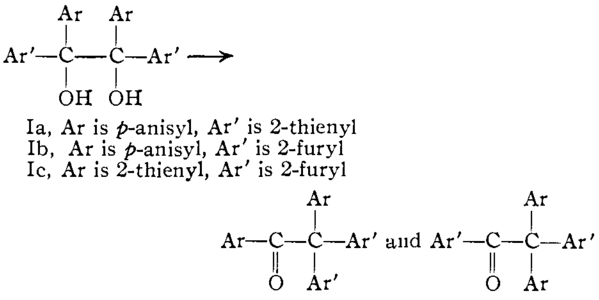
It has been shown in previous reports[1] that the migratory aptitudes of the 2- and 3-pyridyl groups are very small compared to that of the phenyl group, while the migratory aptitudes of the 2-thienyl, the 2,5-dimethyl-3-thienyl and the 2-furyl groups are very large compared to that of the phenyl group. This is to say, rearrangement of symmetrical benzopinacol analogs containing two phenyl groups with two groups of the type in question gave only one pinacolone in each case.

In such one-sided rearrangements, the relationship obtained is merely a qualitative one, for no numerical migratory aptitudes can be calculated. It seemed likely that, for those groups where the migratory aptitudes are very large, numerical values could be obtained by relating the groups in question indirectly to the phenyl group through comparison with the *p*-anisyl group whose migratory aptitude of 500, according to Bachmann and Ferguson,[2] was the highest known up to the time of the present investigation.

Accordingly, in the expectation that their rearrangement would furnish mixtures of pinacolones, the three pinacols of Fig. 1 were synthesized.

An attempt was made to arrive at compound Ia by reducing anisyl thienyl ketone with zinc and acetic acid. This gave rise only to a small yield of what was evidently the corresponding tetraarylethylene according to the elementary analysis. Treatment of thenil with anisylmagnesium bromide gave a tar but the action of thienylmagnesium bromide on anisil furnished a fair yield of Ia.

The pinacol was rearranged using two different media: (1) a refluxing mixture of acetic acid, acetyl chloride and benzene and (2) a refluxing solution of iodine in acetic acid. The pinacolone resulting in larger quantity was isolated and the triarylmethane resulting in larger quantity from the degradation of the mixture of pinacolones was characterized by independent synthesis. The acids from this degradation, which, from the standpoint of accurate analysis, form the important part of the degradation products, were not separated from one another, but were analyzed as mixtures by four independent methods. Each analysis showed nearly the same result, *i.e.*, two moles of anisic acid were present for every mole of thenoic acid. This means that the 2-thienyl group migrated twice as readily as the *p*-anisyl group. Thus, the migratory aptitude of the 2-thienyl group has been established as 1,000.



$$\mathrm{Ar'{-}\overset{Ar}{\underset{OH}{C}}{-}\overset{Ar}{\underset{OH}{C}}{-}Ar'} \longrightarrow$$

Ia, Ar is *p*-anisyl, Ar' is 2-thienyl
Ib, Ar is *p*-anisyl, Ar' is 2-furyl
Ic, Ar is 2-thienyl, Ar' is 2-furyl

$$\mathrm{Ar{-}\underset{O}{\overset{\|}{C}}{-}\overset{Ar}{\underset{Ar'}{C}}{-}Ar'} \text{ and } \mathrm{Ar'{-}\underset{O}{\overset{\|}{C}}{-}\overset{Ar}{\underset{Ar}{C}}{-}Ar'}$$

Fig. 1.

In an effort to synthesize the pinacol of Compound Ib, anisil was treated with furylmagnesium iodide. The product was, unaccountably, anisyl furyl ketone, but anisylmagnesium bromide reacted with furil to give a good yield of Ib. The synthesis of compound Ic, proceeded in a similar manner since thienylmagnesium bromide reacted with furil to give a fair yield.

Unfortunately, the rearrangements of these last two pinacols did not proceed smoothly. The subjection of Ib and Ic to the conditions of rearrangement and then scission produced only a low yield of pure anisic acid in the first case, and only a low yield of nearly pure thenoic acid in the second. These results may provide some indication that the furyl group migrates much more readily than the thienyl group, but the conclusion is by no means a rigid one.

Experimental

1,2-Di-(2-thienyl)-1,2-di-(4-methoxyphenyl)-ethylene.—A 10.0-g. (0.0246 mole) sample of 2-thienyl *p*-anisyl ketone[3] dissolved in 100 ml. of glacial acetic acid was treated with 10.0 g. of zinc dust and allowed to stand for ten days with occasional shaking and addition of 1.0 g. of fresh zinc dust every day. The excess zinc dust was separated from the dark red solution and added dropwise to one liter of ice-water with vigorous stirring. The resulting precipitate was separated by filtration, washed with water and dried. The red powder weighed 9.0 g.

A 1.0-g. sample of this powder was dissolved in 20 ml. of dry benzene, 25 ml. of petroleum ether (b.p. 60–75°) was added, the solution filtered and passed through an alumina column. The column was developed with benzene–petroleum ether mixtures to the point where the first colored band was just about to be eluted. Changing to a 90% solution of dry benzene in petroleum ether, washing until the yellow band had been completely eluted and evaporation of this eluate left a residue of 0.16 g. (16%) of orange semisolid. This was recrystallized three times from a 2-propanol–chloroform mixture to give fine needles of 1,2-di-(2-thienyl)-1,2-di-(4-methoxyphenyl)-ethylene melting at 213.5° dec.

Anal. Calcd. for $C_{24}H_{20}O_2S_2$: C, 71.23; H, 5.00; S, 15.85. Found: C, 70.92; H, 5.02; S, 15.64.

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[1] M. R. Kegelman and E. V. Brown, THIS JOURNAL, **75**, 4649 (1953); **75**, 5961 (1953).

[2] W. E. Bachmann and J. W. Ferguson, *ibid.*, **56**, 2081 (1934).

[3] Ng. Ph. Buu Hoi, Ng. Hoan and Ng. D. Xuong, *Rec. trav. chim.*, **69**, 1083 (1950).

1,2-Di-(2-thienyl)-1,2-di-(4-methoxyphenyl)-ethane-1,2-diol.—A solution of 2-thienylmagnesium bromide was prepared from 2.91 g. (0.12 mole) of magnesium turnings and 19.6 g. (0.12 mole) of freshly distilled 2-bromothiophene dissolved in 120 ml. of absolute ether, and treated at −10° with 8.1 g. (0.03 mole) of anisil[4] in small portions over a five-minute period. The mixture was stirred while being allowed to warm to room temperature, and was then allowed to stand for two days. After hydrolysis, the organic layer was separated, washed twice with water, twice with sodium bicarbonate solution and twice with water. The solution was dried over sodium sulfate and the solvent evaporated *in vacuo* at room temperature under nitrogen. There remained a solid tan residue of crude pinacol which was recrystallized from ethanol, using Norit, to furnish a 4.54 g. (35%) yield of nearly pure pinacol. For analysis, a small sample of this material was recrystallized three times more from absolute ethanol. The resulting white crystals melted at 139.0–139.5°.

Anal. Calcd. for $C_{24}H_{22}O_4S_2$: C, 65.71; H, 5.07; S, 14.62. Found: C, 65.40, 65.42; H, 5.44, 5.07; S, 14.60.

Rearrangement of 1,2-Di-(2-thienyl)-1,2-di-(4-methoxyphenyl)-ethane-1,2-diol and Scission of the Pinacolone. (Method 1).—A 2.20-g. (0.005 mole) sample of this pinacol was refluxed in a mixture of 40 ml. of dry benzene, 10 ml. of glacial acetic acid and 20 ml. of acetyl chloride for 44 hours while protected by a drying tube. The bulk of the volatile material was then removed *in vacuo* (bath at 90°) and the residue freed of the last of the acidic acid by storage in a vacuum desiccator over potassium hydroxide.

The resulting pinacolone residue was next refluxed for 36 hours with a solution of 3.0 g. of potassium hydroxide in 50 ml. of absolute ethanol, whereupon most of the ethanol was then removed *in vacuo* (bath at 90°) and the last traces removed by storage in a vacuum desiccator over sulfuric acid. The residue was dissolved by adding 50 ml. of benzene and 50 ml. of water and shaking thoroughly.

The benzene layer was washed with water, dried and evaporated *in vacuo* at room temperature to leave a dark semi-solid residue which was extracted with ethanol and treated with Nuchar C-190-N. The resulting pale yellow solution after standing for two weeks deposited white crystals. The resulting 0.50 g. of crude di-(2-thienyl)-4-methoxyphenylmethane melted at 88.0–90.0°. After two recrystallizations from ethanol the pure white crystals of triarylmethane melted at 91.5–92.0° and showed no depression in melting point when mixed with an authentic sample of the compound prepared as described below.

The aqueous layer from the extraction of the scission residue was acidified with hydrochloric acid and the precipitate, together with the supernatant liquid, was exhaustively extracted with ether, which was then evaporated. The resulting crystalline residue was sublimed at 10 mm. (bath temperature 130°). Data concerning the mixture of acids obtained are given in Tables I and II.

TABLE I

PROPERTIES OF MIXTURES OF ACIDS

	Method 1	Method 2
Yield, g.	0.62	0.51
Yield, %	87	82
M.p., °C.	108.0–159.5	107.5–159.5
C, %	58.51	....
H, %	4.86	....
S, %	7.17	....
OCH₃, %	14.50	14.24
Neut. equiv.	145.0	145.0

TABLE II

CALCULATION OF PROPORTIONS OF ACIDS (METHOD 1)

Basis of calcn.	Weight %		Mole %		Moles anisic/mole thenoic
	Anisic	Thenoic	Anisic	Thenoic	
C, %	71.6	28.4	67.9	32.1	2.11
S, %	71.4	28.6	67.8	32.2	2.11
OCH₃, %	71.1	28.9	67.4	32.6	2.07
Neut. equiv.	70.0	30.0	68.3	33.7	1.97

(**Method 2**).—A 2.20-g. (0.005 mole) sample of the pinacol was refluxed for 30 minutes with a solution of 1.0 g. of iodine in 100 ml. of glacial acetic acid, cooled, poured into an excess of dilute sulfurous acid and the precipitate was filtered, washed with water and dried to give 2.02 g. (96%) of crude pinacolone which melted at 62–75°.

A 0.2-g. sample of this mixture of pinacolones was withdrawn and recrystallized twice from methanol. The resulting pure 4-methoxyphenyl di-(2-thienyl)-4-methoxyphenylmethyl ketone (?) melted at 152.5–153.0°.

Anal. Calcd. for $C_{24}H_{20}O_3S_2$: C, 68.55; H, 4.81. Found: C, 68.58; H, 5.06.

The remaining 1.82 g. of pinacolones was cleaved by treatment with alkali as described above in method 1. Data concerning the mixture of acids obtained are given in Tables I and III.

TABLE III

CALCULATION OF PROPORTIONS OF ACIDS (METHOD 2)

Basis of calcn.	Weight %		Mole %		Moles anisic/mole thenoic
	Anisic	Thenoic	Anisic	Thenoic	
% OCH₃	69.8	30.2	66.0	34.0	1.94
Neut. equiv.	70.0	30.0	66.3	33.7	1.97

In this case, however, the crude triarylmethane fraction was extracted with three portions of hot petroleum ether (b.p. 30–60°) rather than with ethanol. The solvent was evaporated from the decanted extracts; the residue from the first extract remained oily even after prolonged standing, while those from the second and third crystallized almost immediately upon cooling to form tan rosettes. These two fractions of crystals were each recrystallized three times from ethanol, using Nuchar-C-190-N, to give white needles melting at 91.5–92.0°. A mixture of this material with an authentic sample of di-(2-thienyl)-4-methoxyphenylmethane showed no depression in melting point.

Di-(2-thienyl)-4-methoxyphenylmethane.—To 20.0 g. of phosphorus pentoxide was added a solution of 13.6 g. (0.10 mole) of 4-methoxybenzaldehyde and 16.8 g. (0.20 mole) of freshly distilled thiophene in 50 ml. of petroleum ether (b.p. 30–60°). After standing for one day, the clear red solution was decanted from the solid and the latter washed with a little petroleum ether. The combined solutions were washed with water, sodium carbonate solution and water, the solvent removed and the residue fractionated *in vacuo*. After a forerun of anisaldehyde, a yellow oily distillate of triarylmethane, b.p. 165° (0.4 mm.), was collected.

The crude material crystallized immediately upon cooling and weighed 0.74 g. (2.6%). Recrystallization from ethanol, using Nuchar C-190-N, furnished white needles of di-(2-thienyl)-4-methoxyphenylmethane melting at 91.5–92.0°.

Anal. Calcd. for $C_{16}H_{14}OS_2$: C, 67.11; H, 4.93; S, 22.38. Found: C, 67.11; H, 5.21; S, 22.08.

2-Furyl 4-Methoxyphenyl Ketone from Anisil and 2-Furylmagnesium Iodide.—A solution of 2-furylmagnesium iodide[5] prepared from 30.3 g. (0.156 mole) of 2-iodofuran[5] was filtered quickly, added to 100 ml. of dry benzene and cooled to 0° while protected by a drying tube. With vigorous mechanical stirring, there was then added in small portions 10.5 g. (0.039 mole) of anisil.[4] After standing for two days it was hydrolyzed with ammonium sulfate solution, the organic layer was separated, washed, dried and the ether evaporated *in vacuo*. The residue was extracted with ethanol, the extract evaporated to a small volume and cooled. Water was added dropwise, with stirring, until no further precipitate formed to give 7.6 g. of tan crystals (96% based on anisil in a mole-for-mole ratio) of crude ketone melting at 57–60°. Two recrystallizations from petroleum ether (b.p. 30–60°) furnished fine needles of pure 2-furyl-4-methoxyphenyl ketone melting at 63.5–64.0°.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99. Found: C, 71.31; H, 4.65.

A mixture of this material with an authentic sample[6] of the ketone showed no depression in melting point

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(4) B. B. Corson and R. W. McAllister, THIS JOURNAL, **51**, 2822 (1929).

(5) H. Gilman, H. E. Mallory and G. F. Wright, *ibid.*, **54**, 733 (1932).

(6) L. Maxim and S. Popescu, *Bull. soc. chim. Romania*, **16**, 89 (1934).

The oxime of the material produced in the anomalous reaction, melting at 138.5–139.5°, showed no depression in melting point when mixed with an authentic sample.(7)

1,2-Di-(2-furyl)-1,2-di-(4-methoxyphenyl)-ethane-1,2-diol.—A solution of 4-methoxyphenylmagnesium bromide (0.20 mole) was cooled to −7° and treated with 9.5 g. (0.05 mole) of 2,2′-furil.(8)

Hydrolysis was then effected by shaking with cracked ice. The precipitated salts were dissolved by adding concentrated ammonium chloride solution. The gray solid which remained undissolved was combined with a small amount of material obtained from the organic layer by evaporation. This crude pinacol was recrystallized from ethanol to give 8.2 g. (51%) of nearly pure 1,2-di-(2-furyl)-1,2-di-(4-methoxyphenyl)-ethane-1,2-diol melting at 144.0–145.0°. For analysis, the material was recrystallized once more from ethanol. The resulting white crystals melted at 144.5–145.5°.

Anal. Calcd. for $C_{24}H_{22}O_6$: C, 70.90; H, 5.47. Found: C, 71.06; H, 5.48.

When this pinacol was subjected to the conditions of rearrangement and degradation outlined previously under method 1 and method 2, the only product which could be isolated was anisic acid, which sublimed at 10 mm. and a bath temperature of 150° and melted at 179–181°. The material showed no depression in melting point when mixed with an authentic sample. The yields were 4.9 and 14%, respectively.

1,2-Di-(2-furyl)-1,2-di-(2-thienyl)-ethane-1,2-diol.—The method of preparation was the same as that for the pinacol containing the 4-methoxyphenyl and the 2-thienyl groups. Starting with 0.16 mole of 2-bromothiophene there resulted 15.1 g. of crude crystalline pinacol. This was treated with decolorizing charcoal in boiling benzene, filtered and treated with petroleum ether (b.p. 60–75°). After standing overnight there had deposited 5.5 g. (38%) of nearly pure crystals of 1,2-di-(2-furyl)-1,2-di-(2-thienyl)-ethane-1,2-diol melting at 115°. For analysis, a small sample of this material was recrystallized from benzene–petroleum ether mixture.

Anal. Calcd. for $C_{18}H_{14}O_4S_2$: C, 60.32; H, 3.95; S, 17.88. Found: C, 60.33, 60.38; H, 3.77, 3.77; S, 17.98.

After this pinacol had been subjected to the previously described conditions for rearrangement and degradation, the acid fraction was found to consist only of a low yield of what was evidently thenoic acid contaminated with some other material, perhaps furoic acid. The yields were 12 and 8.5%, respectively. The data are given in Table IV.

TABLE IV

	M.p., °C.	Analyses, % C	H	S
Lit. or calcd. for thenoic acid	126.5	46.84	3.15	25.01
Lit. or calcd. for furoic acid	133–134	53.57	3.80	0.00
Acid from method 1	112.5–122.0	48.50	3.89	23.15
Acid from method 2	113.0–122.5	48.73	3.81	23.20

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(7) L. Vargha and F. Gonszy, THIS JOURNAL, **72**, 2738 (1950).

(8) W. W. Hartman and J. B. Dickey, *ibid.*, **55**, 1228 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

Molecular Rearrangements. IV. The Pinacol Rearrangement of 1-Hydroxy-1-cyclohexylmethylphenylcarbinol[1]

BY GLORIA G. LYLE, RUPERT A. COVEY AND ROBERT E. LYLE

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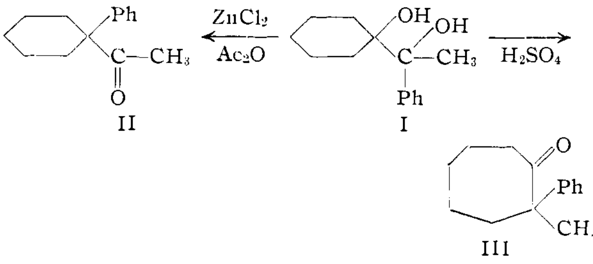
The pinacol rearrangement of 1-hydroxy-1-cyclohexylmethylphenylcarbinol (I) in sulfuric acid has been reinvestigated and the structure of the principal product shown to be 2-methyl-2-phenylcycloheptanone (III). The structure of the second product of the rearrangement has been confirmed by an alternate synthesis as 1-phenyl-1-cyclohexyl methyl ketone (II). A new method of preparation of hydroxy ketones is described.

The pinacol rearrangement of 1-hydroxy-1-cyclohexylmethylphenylcarbinol (I) has been mentioned in three recent publications.[2,3] The two earlier articles[2,3a] indicated that sulfuric acid caused rearrangement of I to form 1-phenyl-1-cyclohexylmethyl ketone (II) while rearrangement in zinc chloride in acetic anhydride resulted in the formation of 2-methyl-2-phenylcycloheptanone (III). Since these results were contradictory to those which would be predicted on the basis of the rearrangement of 1-hydroxy-1-cyclohexyldiphenylcarbinol[4] under similar conditions, a reinvestigation of the pinacol rearrangement of 1-hydroxy-1-cyclohexylmethylphenylcarbinol (I) was initiated in this Laboratory. During the course of this work an abstract of a report by Cauquil[3b] was published which partially corrected the earlier publications; however, there is no record of the isolation or characterization of the pure ketone obtained from the sulfuric acid rearrangement of I.

Rearrangement of I could produce II, III or 1-methyl-1-cyclohexyl phenyl ketone (IV). The synthesis of IV was reported by Russell[2] and by Hamlin and Freifelder,[5] and this ketone proved to be different from any product obtained by the rearrangement of I. Thus since either II or III could be the structure of the rearrangement product and the literature contained several discrepancies, an alternate, unequivocal synthesis of II was developed.



The preparation of II was accomplished by

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[1] This work was supported in part by a Frederick Gardner Cottrell Grant from the Research Corporation of New York.

[2] C. Russell, L. Stroup and J. English, THIS JOURNAL, **74**, 3882 (1952).

[3] G. Cauquil and J. Rouazud, Abstracts of papers presented to Montpellier Section, France, March 27, 1953, and May 22, 1953. (a) *Bull. soc. chim.*, 671 (1953); (b) *ibid.*, 795 (1953).

[4] R. E. Lyle and G. G. Lyle, THIS JOURNAL, **74**, 4059 (1952).

[5] K. E. Hamlin and M. Freifelder, *ibid.*, **75**, 369 (1953).