The unsaturated acid was hydrogenated with Adams catalyst in glacial acetic acid containing 1% of concd. hydrochloric acid. The theoretical volume of hydrogen was absorbed rapidly. Filtration and evaporation of the solvent at 30 mm. gave a liquid, m. p. 10°, which was converted to a mixture of benzylamine salts, m. p. 92–94°. Repeated fractional crystallization from ligroin (b. p. 85–100°) gave the pure benzylamine salt of the *cis meso* acid II in 15% yield. The *cis meso* acid was also isolated as the *p*-phenylphenacyl ester, but the yield was lower.

Acknowledgment.—We wish to thank Dr. S. Winstein for advice on the work reported in this and the following paper.

Summary

2,5-Dimethylcyclopentanecarboxylic acid exists as four stereoisomers: *cis meso*, *trans meso* and two optically active forms. All of these were obtained from the stereoisomeric 2,5-dimethylcyclopentane-1,1-dicarboxylic acids or esters which were readily synthesized from malonic ester and 2,5-dibromohexane. The racemic form was identified by resolution. The *cis meso* configuration was assigned to that isomer which (a) esterified most slowly, (b) was obtained by hydrogenation over platinum in acid solution from 2,5-dimethyl-1-cyclopentenecarboxylic acid, and (c) could be isomerized by acid to a more stable isomer (the *trans meso*). The ester of the *cis meso* acid was hydrolyzed without isomerization by 100% sulfuric acid, but was completely isomerized to *trans meso* ester by sodium ethylate; on hydrolysis with alcoholic potassium hydroxide it gave only *trans meso* acid. The *cis meso* acid chloride was also isomerized readily. The racemic isomer was converted through the α-bromo acid to 2,5-dimethyl-1-cyclopentenecarboxylic acid.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Hindrance in the Stereoisomeric 2,5-Dimethylcyclopentanecarboxylic Acids and their Esters

BY THOMAS L. JACOBS* AND WARNER H. FLORSHEIM[1]

The stereoisomeric 2,5-dimethylcyclopentanecarboxylic acids offer an excellent opportunity for the study of steric hindrance because the polar influences of the substituents should be constant in reactions involving only the carboxyl group. Models show that the methyl groups interfere with the carboxyl group to different extents in the different isomers and indicate that the *cis meso* acid should be the most hindered. This also seems to be true when an attempt is made to approximate with models the transition states of the esterification and hydrolysis reactions in which hindrance would be expected.

The esterification reaction under the conditions of the Fischer–Speier method has been widely used for investigations of steric hindrance and appears to be especially suitable for the purpose.[2] Fewer studies of the reverse reaction, acid-catalyzed ester hydrolysis, have been made, but it is also useful. Kinetic studies were made of the stereoisomers in both of these reactions and as an example of a reaction in which hindrance would not be expected, the investigation was extended to the formation of phenacyl esters from phenacyl bromide and the sodium salts of the acids. The dissociation constants of the acids were also determined.

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(1) An abstract of part of a thesis submitted by Warner H. Florsheim in partial fulfillment of the requirements for the Ph.D. degree in chemistry, May, 1948. A preliminary report of this work was presented before the Organic Division at the 112th meeting of the American Chemical Society, New York City, September, 1947.

(2) The suitability of this reaction has been discussed by Hughes, *Quart. Rev.*, **2**, 107 (1948), who also gives many of the references to earlier work.

Experimental

The preparation of the 2,5-dimethylcyclopentanecarboxylic acids and their methyl esters was described in the preceding article.[3] Trimethylacetic acid was prepared from *t*-butylmagnesium chloride and carbon dioxide.[4] It was carefully fractionated and the center cut, b. p. 162°, m. p. 34–35°, was used. Some of the pure acid was converted by using diazomethane into methyl trimethylacetate, b. p. 99.5–100°. Ethyl butyrate (Eastman Kodak Co. white label grade) was redistilled, b. p. 117–118°. Phenacyl bromide (Eastman white label grade) was recrystallized four times from ligroin, b. p. 85–100°; the m. p. of the sample used was 57–58°.

Acid-Catalyzed Esterification.—Anhydrous methanol[5] was fractionated carefully and made approximately 0.06 *N* in hydrogen chloride using the pure, dry gas.

The organic acids were weighed into 50-ml. volumetric flasks and placed in a thermostat which was maintained at 40.00 ± 0.01°. The methanol solution at the same temperature was then added and after thorough mixing the reaction was followed by titrating aliquots with standard sodium hydroxide using phenolphthalein as the indicator.

The reaction of methanol and hydrogen chloride, which decreases the catalyst concentration, was a significant factor only in the case of the *cis-meso*-2,5-dimethylcyclopentanecarboxylic acid. An approximate correction was made possible in this case by determining the hydrogen chloride concentrations at various times in a control solution containing no organic acid. These values are given in Table I.

Acid-Catalyzed Ester Hydrolysis.—The method chosen was that of Anantakrishnan and Krishnamurti.[6] The catalyst solution was prepared from 600 g. of pure dioxane[7] and 400 g. of 0.5 *N* hydrochloric acid; it was kept at 40.0°

(3) Jacobs and Florsheim, THIS JOURNAL, **72**, 256 (1949).

(4) "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, New York, N. Y., 1941, p. 524.

(5) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(6) Anantakrishnan and Krishnamurti, *Proc. Indian Acad. Sci.*, **14A**, 270 (1941).

(7) Hess and Frahm, *Ber.*, **71**, 2627 (1938).

TABLE I

THE REACTION OF HYDROGEN CHLORIDE WITH METHANOL AT 40°

Time, hr.	Hydrogen chloride concentration
0	0.05863
6.25	.0576
23.25	.0551
32	.0536
47	.0529
54	.0522
70.5	.0508

and its concentration remained at 0.1643 *N* during the three weeks required for the experiments. The rate measurements were carried out at 40.00 ± 0.01° in approximately the same way as described for the esterification. Values calculated for the first 10% of the reaction were ignored.

The Reaction of Sodium 2,5-Dimethylcyclopentanecarboxylates with Phenacyl Bromide.—Solutions of 0.400-g. samples of the three isomeric 2,5-dimethylcyclopentanecarboxylic acids in 100-ml. volumetric flasks were dissolved in 10 ml. of 95.5% by weight ethanol and titrated to the phenolphthalein end-point with 0.02 *N* sodium hydroxide. The indicator color was just bleached with 0.01 *N* nitric acid and water was added to bring the total volume of water to 33.3 ± 0.1 ml. These solutions were placed in a thermostat at 40.00 ± 0.01° overnight. A 2.242-g. sample of phenacyl bromide was dissolved in 95.5% ethanol at 40.0° to make 100 ml. of solution and a 25-ml. aliquot of this solution was added to each solution of a sodium salt; the latter were then diluted to 100 ml. with 95.5% ethanol at 40.0°. Each hour one 10.00-ml. sample was withdrawn, treated with 10.04 ml. of 0.05074 *N* silver nitrate solution, 5.0 ml. of chloride-free 6 *N* nitric acid and 1 ml. of ferric alum solution. The samples were then titrated with 0.05167 *N* potassium thiocyanate solution.

The ionization constants of the 2,5-dimethylcyclopentanecarboxylic acids were determined with an accuracy of about ± 10% by potentiometric titration with a Beckman direct-reading *p*H meter of solutions in "conductivity water" saturated at 24°. The solubilities of the acids and the ionization constants corrected for the activity coefficients of the acid anions as calculated from ionic strengths in the usual way are given in Table II.

TABLE II

IONIZATION CONSTANTS AND SOLUBILITIES IN WATER OF 2,5-DIMETHYLCYCLOPENTANECARBOXYLIC ACIDS AT 24°

Acid	Ionization constant	Solubility, g./l.
Meso trans	2.06×10^{-5}	1.66
Racemic	1.18×10^{-5}	3.34
Meso cis	0.40×10^{-5}	2.11

Results and Discussion

The rate constants for the acid catalyzed esterifications were calculated by the integrated expression of Goldschmidt[8] in which the change in the catalyst due to formation of water in the esterification is taken into account.

$$k = \frac{(a + r)2.303 \log [a/(a - x)] - x}{(\text{catalyst})rt}$$

In this expression a is the original concentration of organic acid, x is the concentration of ester formed after time t, and r is an empirical constant.[8,9,10] The results are given in Table III and a typical run is detailed in Table IV. The value of r at 40° was taken as 0.32 in agreement with Smith[10] since he presented more data useful for comparison, but the values of k are not very sensitive to changes in r, and the average deviation in the k values is about the same if Williamson and Hinshelwood's value of $r = 0.36$ is used. This results in slightly lower values for k; for example with the *trans meso* acid the value drops from 0.00492 to 0.00486.

TABLE III

RATE CONSTANTS FOR THE ACID CATALYZED ESTERIFICATION OF 2,5-DIMETHYLCYCLOPENTANECARBOXYLIC ACIDS IN METHYL ALCOHOL AT 40.00°

Acid	HCl concn.	a	$k \times 10^3$ l. m.$^{-1}$ sec.$^{-1}$
Trimethylacetic	0.05947	0.1976	5.55 ± 0.05
Meso trans	.05727	.08271	4.93 ± .10
		.1065	4.92 ± .07
Racemic	.05884	.09592	0.612 ± .006
		.07530	0.624 ± .013
Meso cis	.05863	.08891	0.0232 ± .0018

TABLE IV

ESTERIFICATION OF *meso-trans*-2,5-DIMETHYLCYCLOPENTANECARBOXYLIC ACID WITH METHANOL AT 40°

a = 0.1065, HCl catalyst = 0.07527

t, sec.	$a - x$	$k \times 10^3$
900	0.0838	4.84
1800	.0663	4.91
2400	.0574	4.88
3000	.0501	4.82
3600	.0433	4.86
4200	.0374	4.90
4800	.0319	4.99
5400	.0269	5.12
6000	.0247	4.93

With the *cis meso* acid, which required seventy hours for 24% esterification, account was taken of the reaction between methanol and hydrogen chloride by assuming that the rate of this reaction was not influenced by the presence of the organic acid, and using an average value of the hydrogen chloride concentration for each time value. This gives an average value of $k = 0.0232 \times 10^{-3}$ instead of 0.0219×10^{-3} obtained by using the initial value of the hydrogen chloride concentration in the equation. In this experiment the values of k dropped off somewhat with time used when the adjusted catalyst concentrations were even.

The acid-catalyzed hydrolysis of the methyl esters was carried out in aqueous dioxane because solutions of hydrogen chloride are stable in this solvent.[6] Ethyl butyrate was run to check the value obtained by Anantakrishnan and Krishnamurti[6] and methyl trimethylacetate was meas-

(8) Goldschmidt, *Ber.*, **29**, 3220 (1895).

(9) Williamson and Hinshelwood, *Trans. Faraday Soc.*, **30**, 1145 (1934).

(10) Smith, THIS JOURNAL, **61**, 254 (1939).

ured for comparison. The pseudo first order rate constants were calculated by the usual integrated expression.

The results are given in Table V.

TABLE V

RATE CONSTANTS FOR THE ACID CATALYZED HYDROLYSIS OF METHYL 2,5-DIMETHYLCYCLOPENTANECARBOXYLATES IN 60% DIOXANE AT 40.00°

Concn. of HCl 0.1643 M, a = 0.08 to 0.20

Ester	$k \times 10^5$ l. mole^{-1} sec.$^{-1}$
Ethyl butyrate[a]	9.3 ± 0.3
Methyl trimethylacetate	1.08 ± 0.04
Methyl 2,5-dimethylcyclopentanecarboxylates	
Meso trans	0.94 ± 0.04
	.95 ± .02
Racemic	.32 ± .02
	.29 ± .02
Meso cis	.18 ± .02

[a] Anantakrishnan and Krishnamurti[8] gave values at 60°, 50°, 42° and 35°. When log k is plotted against the reciprocal of the absolute temperature, the first three values fall on a straight line but the 35° value is low. To fall on the line, the 35° value would have to be 5.46 instead of 4.93 × 10^{-5}. From the graph the value of k at 40° was found to be 8.4 × 10^{-5}.

It was established that the *cis meso* ester was not inverted to the *trans meso* during the hydrolysis by recovering the mixture of acid and ester from the rate run, completing the hydrolysis with 100% sulfuric acid[3] and showing that the recovered acid was the *cis meso* isomer of good m. p.

In a preliminary experiment it was shown that the hydrolysis of the methyl esters in 80% aqueous ethanol is a very slow reaction; more than ten days at 80° were required for about 10% completion, and reliable rate constants were not obtained.

Second order rate constants for the reaction of phenacyl bromide with the sodium 2,5-dimethylcyclopentanecarboxylates were calculated from the usual integrated expression in which the concentrations of the reactants are equal. The rate constants are given in Table VI.

TABLE VI

RATE CONSTANTS FOR THE REACTION OF PHENACYL BROMIDE WITH SODIUM 2,5-DIMETHYLCYCLOPENTANECARBOXYLATES IN 60% ETHANOL AT 40°

Concn. sodium salt = concn. phenacyl bromide = 0.02817 M

Sodium salt	$k \times 10^3$ l. mole^{-1} sec.$^{-1}$
Meso trans	2.73 ± 0.09
Racemic	2.93 ± .05
Meso cis	6.47 ± .10

Of the rate measurements reported here, only the acid catalyzed esterification offers a sufficient difference between isomers (two hundred fold between the two *meso* compounds) to be significant. That *meso* isomer which esterifies more slowly is the one for which a *cis* configuration is indicated by hydrogenation and isomerization experiments.[3] Although the kinetic experiments do not permit a choice between the alternative unimolecular and bimolecular mechanisms usually advanced for acid catalyzed esterification and hydrolysis[11] because the alcohol was the solvent, it is likely that the faster isomer (*meso trans*) esterifies by the usual bimolecular process. This is borne out by the failure of the *meso trans* ester to hydrolyze in 100% sulfuric acid and by preliminary cryoscopic experiments in 100% sulfuric acid, where this isomer gave a normal van't Hoff "*i*" factor of 2.[12,13] The *cis meso* isomer may esterify partly by the unimolecular mechanism, since it gave a van't Hoff "*i*" factor of 2.3 but insufficient material was available to examine this possibility. It is also possible that the unimolecular mechanism makes some contribution in the esterification of the *meso trans* and racemic isomers.

The variation in the rate constants for the acid-catalyzed hydrolysis of the methyl esters was only five-fold. Although the conditions for the hydrolysis were very different from those for esterification, it is somewhat surprising to find so small a spread since the variation with structure is usually comparable in the two reactions. Thus, ethyl acetate[6] is hydrolyzed 20 times faster than ethyl trimethylacetate while acetic acid is esterified 27 times faster than trimethylacetic acid with methanol at the same temperature.[14] Nevertheless it is possible that in the highly hindered *cis meso* compounds there is greater strain in the ester than in the acid due to interference of the ester methyl group with the hindering ring substituents. The resulting higher rate of ester hydrolysis for this isomer relative to the *meso trans* ester would account for smaller spread in the rates of hydrolysis. It would also be apparent as a shift of the equilibrium constant toward the acid and alcohol with the *cis meso* compounds relative to the *trans meso* or racemic. This will be examined later. An alternative explanation is that in aqueous dioxane, a more polar solvent, the unimolecular mechanism for the *cis meso* compounds is more important than in absolute methanol.

It is interesting that the slowest isomer studied here is esterified more readily than diisopropylacetic acid, the most nearly similar aliphatic compound. A preliminary rate measurement on the latter gave a value of about 2 × 10^{-6} l. mole^{-1} sec.$^{-1}$ at 40°.[15]

The experiments with phenacyl bromide and the sodium 2,5-dimethylcyclopentanecarboxylates

(11) Day and Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

(12) Treffers and Hammett, THIS JOURNAL, **59**, 1708 (1937).

(13) Newman, Kuivila and Garrett, *ibid.*, **67**, 704 (1945).

(14) Smith, *ibid.*, **62**, 1136 (1940).

(15) von Braun and Fischer, *Ber.*, **66**, 101 (1933). Mr. Russell Reed has prepared this acid again and details of its esterification and other reactions will be reported later.

serve merely to establish that in a reaction which does not involve the hindered carbon the rates are comparable. No explanation is obvious for the fact that the *cis meso* isomer reacts somewhat more rapidly.

These experiments will be extended to other temperatures and the mechanisms of the reactions will be examined more closely when more material is available.

Summary

The rates of the acid-catalyzed esterification with methanol of the stereoisomeric 2,5-dimethylcyclopentanecarboxylic acids, the acid-catalyzed hydrolysis of the corresponding methyl esters, and the reaction of the sodium salts with phenacyl bromide were measured at 40°. The isomer believed to be the *trans meso* acid esterified two hundred times faster than the *cis meso* acid. The rate variation in the hydrolysis was only five-fold and in the reaction of phenacyl bromide with the sodium salts, the *cis meso* compound reacted about twice as fast as the other two. The *meso trans* isomer reacted at about the same rate as trimethylacetic acid or ester in the esterification and hydrolysis, but all isomers reacted more slowly than diisopropylacetic acid or ester, the most nearly similar aliphatic compound.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Polynuclear Aromatic Hydrocarbons. I. Methyl-1,2-benzanthracenes[1]

BY MELVIN S. NEWMAN* AND RUSSELL GAERTNER†

Although many polynuclear aromatic hydrocarbons and their derivatives have been prepared and evaluated as to physiological action, there has not yet emerged a true correlation of carcinogenic activity with any other known property of these molecules. This has been due in part to the fact that investigators have not had sufficient access to whole series of compounds and have had to conduct their experiments with relatively few members. Accordingly we have undertaken to make all twelve of the monomethyl-1,2-benzanthracenes and the six monomethylbenzo[c]phenanthrenes in large enough amounts so that research workers may initiate experiments with the assurance that all of these compounds will soon be available. It is hoped that all members of each series will be tested for carcinogenic activity by several methods so that a more significant evaluation of the carcinogenic potency can be made than is possible at present.[2]

This communication describes the methods used to prepare appreciable quantities of 1,2-benzanthracene, of 9,10-dimethyl-1,2-benzanthracene and of 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 2′- and 3′-methyl-1,2-benzanthracenes. Since our main objective was the preparation of sufficient quantities of these materials for biological evaluation, we do not claim to have found the best methods for preparing each of the compounds herein listed. However, several improvements over literature syntheses have been made and recorded. All of these hydrocarbons had been prepared previous to the start of this work. The melting points of all of the monomethyl-1,2-benzanthracenes have been listed.[3] Since that publication the following additional syntheses (through 1948) have been reported: 3-methyl-,[4] 4-methyl-,[5a,b] 5-methyl-,[6a,b] 6-methyl-,[7] 8-methyl-,[8a,b] 9-methyl-,[9a,b] 10-methyl-,[10a,b,c,d,e,f] 1′-methyl-,[11] 2′-methyl-,[12] 4′-methyl.[13] The only significant change in properties over those listed previously[3] is in the case of 8-methyl-1,2-benzanthracene which has a melting point of 118.0–118.5°[8a,b] instead of 107°.[3]

The syntheses of 1,2-benzanthracene according to Badger and Cook[14] and of 10-methyl-1,2-benz-

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(2) The compounds herein described are being evaluated by Dr. I. Berenblum at the National Cancer Institute, Bethesda, Md.

(3) J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938).

(4) M. S. Newman and R. T. Hart, THIS JOURNAL, **69**, 298 (1947).

(5) (a) L. F. Fieser and R. N. Jones, *ibid.*, **60**, 1942 (1938); (b) W. E. Bachmann, M. W. Cronyn and W. S. Struve, *J. Org. Chem.*, **12**, 596 (1947).

(6) (a) W. E. Bachmann and A. L. Wilds, THIS JOURNAL, **60**, 624 (1938); (b) W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

(7) W. E. Bachmann and J. M. Chemerda, *ibid.*, **6**, 36 (1941).

(8) (a) L. F. Fieser and Wm. S. Johnson, THIS JOURNAL, **61**, 168, 1647 (1939); (b) (Mrs.) J. W. Cook, A. M. Robinson and E. M. F. Roe, *J. Chem. Soc.*, 266 (1939).

(9) (a) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **62**, 49 (1940); (b) C. K. Bradsher, *ibid.*, **62**, 1077 (1940).

(10) (a) L. F. Fieser and J. L. Hartwell, *ibid.*, **60**, 2555 (1938); (b) L. F. Fieser and E. B. Hershberg, *ibid.*, **61**, 1272 (1939); (c) A. Dansi and C. Ferri, *Gazz. chim. ital.*, **69**, 195 (1939); (d) J. L. Wood and L. F. Fieser, THIS JOURNAL, **62**, 2674 (1940); (e) B. M. Mikhailow, *Izvest. Akad. Nauk S. S. S. R., Otdel Khim. Nauk*, 619 (1946); *C. A.*, **42**, 6351d (1948); (f) B. M. Mikhailow and T. K. Kozminskaya, *Doklady Akad. Nauk S. S. S. R.*, **59**, 509 (1948); *C. A.*, **42**, 6792e (1948).

(11) W. E. Bachmann and R. O. Edgerton, THIS JOURNAL, **62**, 2550 (1940).

(12) W. E. Bachmann and G. D. Cortes, *ibid.*, **65**, 1329 (1943).

(13) A. Sempronj, *Gazz. chim. ital.*, **70**, 615 (1940).

(14) G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 802 (1939).