Mixed Carboxylic Anhydrides in the Friedel–Crafts Reaction[1]

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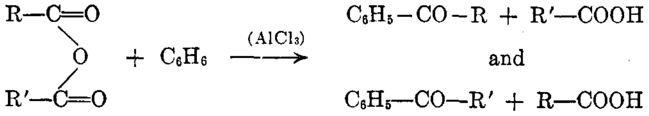
Received July 19, 1962

The behaviors of eleven mixed acetic anhydrides in the Friedel–Crafts ketone synthesis have been investigated, under conditions designed to reveal relationships between the characteristics of the competing acyl groups and their relative efficiencies in such acylations. A comparative study has been made of the behaviors of mixtures of the two simple anhydrides, and mixtures of the two acyl chlorides, corresponding to two of these mixed anhydrides; ketone ratios varied widely with variation in the type of acylating agent. Formic acetic anhydride gave methyl ketones, but no aldehydes.

Acylations with mixed carboxylic anhydrides, using limited quantities of the other reagents, place the two halves of each anhydride in direct mutual competition. In a Friedel–Crafts process, the two possible reactions are



The relative yields of the two ketones, therefore, should reflect the respective influences of the two differing acyl groups.

Most early work with mixed anhydrides, in reactions of this and other types, was rather sporadic, was not done in a manner calculated to reveal any broad patterns of behavior which might exist, and led to diverse and sometimes contradictory results and inferences. In recent years the reactions with amines and alcohols have received more thorough and fruitful attention,[2–6] but there have been comparatively few reports of their behavior in the Friedel–Crafts reaction.[7–11] In two papers which described acylations of this type with a number of mixed anhydrides, the ketone of lower molecular weight was reported to be the invariable predominant product by one group of authors,[8] who used all-aromatic anhydrides, while the ketone of higher molecular weight was found to predominate in most instances by the other group,[9] who used mixed acetic anhydrides, including several of those studied in the present work.

The present paper describes the Friedel–Crafts acylation of benzene with eleven mixed acetic anhydrides under standard conditions, and also under certain varied conditions. It compares the behaviors of two of them with those of equimolar mixtures of (a) the corresponding simple anhydrides, and (b) the corresponding acyl halides. Earlier workers usually used large excesses of benzene to serve as both reagent and solvent, adding their anhydrides gradually to the mixture of hydrocarbon and catalyst. This compromised any deductions concerning the competitive natures of the two acyl radicals which might have been drawn from the results, since their final products presumably included not only the quantities of ketones formed by the initial reactions of the anhydrides, but also substantial additional amounts of the same products, resulting from subsequent reactions between the excess benzene and the carboxylic acids released in the initial steps. In the present work, equimolar quantities of mixed anhydride and benzene reacted in carbon disulfide, the benzene being added dropwise to a cooled mixture of anhydride, solvent and catalyst, so that hydrocarbon was never present in excess. This procedure minimized opportunities for secondary reactions, though it did not preclude them; consequently, each molar ratio of the two ketonic products was more nearly a true measure of the relative ketone-forming abilities of the two halves of the mixed anhydride itself.

In most work involving mixed carboxylic anhydrides, there is a recognized uncertainty factor resulting from their tendency to disproportionate into the two simple anhydrides, and from the lack of practical and reliable absolute methods for determining the extent of this disproportionation at the time of their actual use. Some degree of compromise is necessary in purifying them, since such normal operations as distillation and washing may accelerate this shift, and thus defeat their own purpose; no one procedure is best for the purification of all mixed anhydrides, or even for all members of the same series. The methods described for the preparation, purification, analysis, and use of each one employed here were selected after much experimental study; though no great precision is claimed, we believe that they were successful enough to make the results significant.

Table I shows the results of acylations with mixed anhydrides under the selected standard conditions. Its most evident feature is the substantial, and all but general, predominance of the higher ketone, in the mixture of two ketonic products formed from each mixed anhydride. It is not possible, however, to dismiss the ketone-forming efficiency of each acyl group as a simple function of either its chain length or its total size. There are obvious quantitative departures from such a pattern, and acetic chloracetic anhydride reverses it sharply. Collateral work in this laboratory[12] with aromatic, and aliphatic–aromatic mixed anhydrides, showed other reversals. Acetic *p*-nitrobenzoic anhydride, for example, gave principally acetophenone when it reacted with benzene.

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[1] Part of this paper was abstracted from the M.S. thesis of E. C. Sibille, Louisiana State University, August, 1959.

[2] C. D. Hurd and M. F. Dull, *J. Am. Chem. Soc.*, **54**, 3427 (1932).

[3] C. D. Hurd and A. S. Roe, *ibid.*, **61**, 3355 (1939).

[4] A. R. Emery and V. Gold, *J. Chem. Soc.*, 1443 (1950).

[5] N. A. Leister and D. S. Tarbell, *J. Org. Chem.*, **23**, 1152 (1958).

[6] P. S. Bailey and Y. G. Chang, *ibid.*, **27**, 1192 (1962).

[7] J. Cryer, *Trans. Roy. Soc. Can. III*, **19**, 29 (1925).

[8] J. M. Zeavin and A. M. Fisher, *J. Am Chem. Soc.*, **4**, 3738 (1932).

[9] J. W. Williams, Y. J. Dickert, and J. A. Krynitsky, *ibid.*, **63**, 2510 (1941).

[10] E. Berliner, *Org. Reactions*, **V**, 242 (1949).

[11] D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957). Structural peculiarities of the anhydrides discussed in ref. 10 and 11 make them imperfectly analogous to those in the present work.

[12] K. P. Kammann, Jr., M. S. thesis, Louisiana State University, 1960.

TABLE I

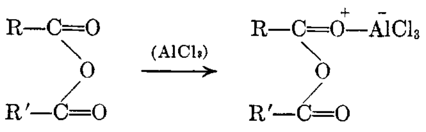
ACYLATIONS OF BENZENE WITH MIXED ACETIC ANHYDRIDES[a]
Three Hours, at 0–5°

Mixed acetic anhydride[b]	Total ketone yield, %	Mole % of each ketone in total ketone product	
		Higher ketone	Acetophenone
Propionic	66.9	65.5	34.5
Butyric	71.0	72.9	27.1
Valeric	76.7	80.1	19.9
Caproic	75.0	72.1	27.9
Heptanoic	65.5	75.1	24.9
Octanoic	64.6	74.1	25.9
Isobutyric	61.0	60.9	39.1
α-Methylbutyric	56.3	69.8	30.2
β-Methylbutyric	61.7	80.7	19.3
Chloroacetic	77.6	10.8	89.2

[a] Molar ratios, anhydride–benzene–$AlCl_3$ were 1:1:3(+). [b] Formic acetic anhydride, in numerous runs under varied conditions (which included use of other aromatic compounds and other catalysts) produced only methyl ketones, usually in mediocre yields, and failed to produce aldehydes.

It might appear that the relative strengths of the two acids represented in each anhydride were the determining factors, with the ketone corresponding to the weaker acid being formed in greater quantity. This generalization holds good, qualitatively, for the compounds in Table I, and for some others, including acetic *p*-nitrobenzoic anhydride. Quantitatively, however, the weaker acid theory is vulnerable. The differences in acid strengths were so small in most cases that they hardly appear to furnish an adequate reason for the substantial differences in ketone proportions. Moreover, if the acids are arranged in inverse order of their pK_a values, this order does not always coincide with a sequence of the same acids listed according to the ketone-forming efficiencies revealed in Table I. Butyric acid, for example, is slightly stronger than propionic, but the predominance of butyrophenone exceeded substantially that of propiophenone.

Such objections may be avoided by ascribing the results to the relative electron-releasing tendencies of the alkyl portions of the competing acyl groups; the ketone formed in greater quantity being the one whose alkyl group was more strongly electron-releasing in the actual nonaqueous system, and in the presence of aluminum chloride. Relatively strong electron release by one alkyl group would favor an initial coördination of aluminum chloride with its adjacent carbonyl oxygen atom, presumably the rate determining step; *i.e.*, if R were more strongly electron-releasing than R′, the bias would be toward



A sequence of acids arranged on this basis would not be necessarily the same as a sequence based on their ionization constants in aqueous solution, and the differences between them might be larger. Hyperconjugative effects, increased in relative importance by the electron demand of the catalyst, could become significant factors.

Since the chloromethyl group was by far the least electron-releasing one represented here, the behavior of acetic chloracetic anhydride deserves special attention. It was not possible to give this anhydride the customary sodium carbonate washing, and though its neutralization eqvivalent was fairly good, elemental analysis showed it to be quite impure. The exceptionally strong predominance of acetophenone in the ketone mixture derived from it, however, was too emphatic to be ignored, even if regarded as a mere approximation. It was consistent with the idea that the relative electron-releasing powers of the alkyl groups were the major factors, with their sizes exerting, at most, only minor influences.

Some modification of this generalization became necessary when steric factors were present. This may be observed in Table II, which presents selected data from Table I, rearranged to facilitate comparisons of the respective influences of unbranched, alpha-branched and beta-branched alkyl groups. The following observations may be made.

TABLE II

BRANCHED *vs.* UNBRANCHED ACYL RADICALS IN FRIEDEL–CRAFTS ACYLATIONS

Mixed acetic anhydride	Mole % of each ketone in total ketone product	
	Higher ketone	Acetophenone
Valeric	80.1	19.9
β-Methylbutyric	80.7	19.3
α-Methylbutyric	69.8	30.2
Butyric	72.9	27.1
Isobutyric	60.9	39.1
Propionic	65.5	34.5

(a) Where total sizes of alkyl groups were the same, beta branching had no significant influence on ketone-forming efficiencies. (Compare valeric with β-methylbutyric).

(b) Alpha branching, on the other hand, made a large and approximately uniform difference. (Compare valeric with α-methylbutyric, and butyric with isobutyric.)

(c) Where chain lengths were the same, but total sizes differed, alpha branching again made significant differences, but smaller ones. (Compare butyric with α-methylbutyric, and propionic with isobutyric.)

(d) Alpha branching reduced the ketone-forming efficiencies of the acyl groups in which it occurred, but not nearly enough to eliminate their predominances over acetyl. It was a factor, but not the major one.

Alpha branching could do three things: (i) increase the inductive electron release of the alkyl group toward the carbonyl carbon; (ii) diminish the hyperconjugative electron release of the alkyl group; and (iii) exercise steric hindrance at one or more steps in the reaction. The results indicated that (i) was relatively unimportant, and that the observed influence of alpha branching should be ascribed to (ii), or (iii), or a combination of both. The insignificance of beta branching is understandable. It would not contribute to (ii), and because of its remoteness from the reaction site it could hardly contribute much to (iii) either.

Table III shows the effects of changing three of the standard experimental conditions. The first of these was reaction time, from the initial addition of benzene to the quenching of the catalyst, all other conditions remaining uniform. Unusual difficulty was experienced in obtaining consistent results when the time was only

TABLE III

INFLUENCES OF REACTION TIME, TEMPERATURE, AND CATALYST QUANTITY ON ACYLATION WITH ACETIC BUTYRIC ANHYDRIDE

Moles $AlCl_3$ per mole anhydride	Reaction time, hr.	Temp., °C.	Total ketone yield, %	Mole % of each ketone in total ketone product: Butyrophenone	Acetophenone
3	0.5	0–5	53.2	69.0	31.0
3	1.5	0–5	62.1	71.1	28.9
3	3.0	0–5	71.0	72.9	27.1
3	8.0	0–5	80.4	74.5	25.5
3	3.0	25	76.2	73.5	26.5
2	3.0	0–5	65.9	55.7	44.3
2[a]	3.0	0–5	68.9	71.4[b]	28.6

[a] Using acetic valeric anhydride. [b] Valerophenone.

half an hour, presumably because slight variations in reagents and procedure exerted relatively high leverage in such a brief and incomplete process. The values recorded for this reaction time are the averages of the results of four runs, in which the mole per cent of butyrophenone ranged from 66.1 to 71.5.

The smallness of the variation in ketone ratios, particularly over the range from 1.5 to 8 hours, showed that predominance of the higher ketone was not a chance result of the arbitrary choice of a standard time. Total yields increased with time, at a gradually diminishing rate of increase. Predominance of the higher ketone increased, slightly but regularly, with increase in time. Since it was this ketone which was being formed in greater quantity from the outset, the total potential supply of butyryl units available for acylation, whatever their nature, underwent a more rapid depletion than the supply of acetyl units; on a simple probability basis, therefore, it might have been expected that in the longer runs, the gap between acetophenone and butyrophenone would narrow. Instead, it widened slightly.

The second part of Table III shows that the molar ratio of ketonic products was nearly indifferent to an increase in the reaction temperature to 25°, though the total yield increased moderately.

The third part of Table III shows the results of reducing the quantity of aluminum chloride from three moles to two, per mole of anhydride. This effect was studied with two different anhydrides, acetic butyric and acetic valeric. In both cases, use of only two moles of catalyst diminished total ketone yields, and reduced the predominances of the higher ketones. The latter observation was somewhat surprising, though it harmonized with the work of Williams[9] on acetic caproic anhydride. Since the reduction in catalyst quantity supposedly enabled only half of each anhydride to qualify for ketone formation, it might have been expected to make the competition more one-sided.

The data in Table IV were obtained by conducting parallel acylations with (a) a mixed anhydride; (b) an equimolar mixture of the two corresponding simple anhydrides; and (c) an equimolar mixture of the two corresponding acyl halides. Comparable conditions were established by using the indicated proportions.

TABLE IV

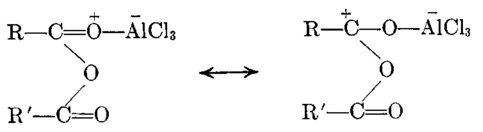
COMPARISONS OF ACYLATIONS WITH MIXED ANHYDRIDES, EQUIMOLAR MIXTURES OF SIMPLE ANHYDRIDES, AND EQUIMOLAR MIXTURES OF ACYL HALIDES

Acylating agent(s)	Molar proportions acylating agent(s):-benzene:$AlCl_3$	Total ketone yield, %	Mole % of each ketone: Higher	Acetophenone
Acetic butyric anhydride	1:1:3	71.0	72.9	27.1
Acetic anhydride and butyric anhydride	(0.5 + 0.5):1:3	76.3	63.6	36.4
Acetyl chloride and butyryl chloride	(1 + 1):1:2	83.7	43.7	56.3
Acetic valeric anhydride	1:1:3	76.7	80.1	19.9
Acetic anhydride and valeric anhydride	(0.5 + 0.5):1:3	73.6	60.2	39.8
Acetyl chloride and valeryl chloride	(1 + 1):1:2	89.0	44.3	55.7

The feature of Table IV was the reversal of predominance of one acyl group over the other when a mixture of acyl halides was employed, acetophenone being formed in higher molar ratios in both instances. The biases were smaller when using acyl halides, and were less affected by change in the identity of the acyl group. It is evident that the mixed anhydrides, in fact, functioned as themselves; that is, that they were not changed into two simple anhydrides, or into an equilibrium mixture of mixed and simple anhydrides, prior to the start of the Friedel–Crafts reaction. It appears, also, that if they underwent a change to acyl halides as a necessary preliminary to the acylation (as proposed by Groggins,[13] and accepted by Gore[14] and others, for carboxylic anhydrides in general) such a change could not have been both rapid and complete.

It is difficult to reconcile Groggins's mechanism with the data in Table IV, which showed that the butyryl and valeryl halves of the mixed anhydrides were much more efficient than the acetyl halves in ketone formation, but that acetyl chloride itself was slightly more efficient than either of the larger acyl chlorides. A possible explanation based on that mechanism might be that the predominance of the higher ketone, when a mixed anhydride was used, was the result of a bias favoring the higher acyl group in one or more of the several steps of the assumed conversion of anhydride to acyl halides, so that butyryl or valeryl chloride became available more rapidly than acetyl chloride.

A more attractive alternative explanation is that the actual acylating agent, when an anhydride is employed, is not (or at least not exclusively) the acyl halide complex. Instead, it may be a complex of the entire anhydride molecule, through one of its carbonyl oxygens, with aluminum chloride.



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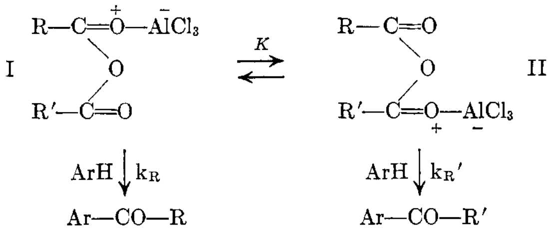
[13] P. H. Groggins and R. H. Nagel, *Ind. Eng. Chem.*, **26**, 1313 (1934).

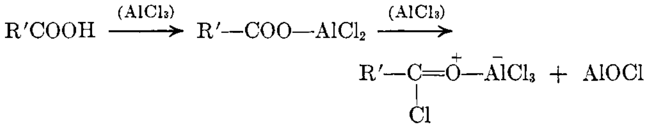
[14] P. H. Gore, *Chem. Rev.*, **55**, 229 (1955).

Such a complex will then be subject to nucleophilic attack by the aromatic component.[15] If this is true, then the essential steps which will determine the proportions of the final products will be



When R is more strongly electron-releasing than R′, the equilibrium constant K will favor structure I. The electrophilic reactivity of II, however, will be greater than that of I; hence the rate constant $k_{R'}$ will exceed k_R. The experimental results indicate that the equilibrium distribution between I and II is more significant than the difference between the rates of nucleophilic displacement, so that coördination of the catalyst with the anhydride is the rate determining step. When the acylating reagent is a mixture of acyl halides, on the other hand, the two steps appear to approach each other in significance, the displacement step serving as the rate determining one in the two cases described here.

This mechanism accounts for the influences of the electron-releasing abilities of R and R′, for the observed steric effects of branching adjacent to a carbonyl carbon atom, and for the marked differences between results obtained with mixed anhydrides, and those obtained with mixtures of acyl halides. While it rejects the first step in Groggins's mechanism (preliminary conversion of anhydrides to acyl halides) it is not incompatible in principle with his proposed later steps. When three moles of catalyst are used, the uncoördinated half of the anhydride, released as a carboxylic acid when the ketone is formed, presumably goes through the sequence



$$R'COOH \xrightarrow{(AlCl_3)} R'{-}COO{-}AlCl_2 \xrightarrow{(AlCl_3)} R'{-}\underset{\underset{\displaystyle Cl}{|}}{C}{=}\overset{+}{O}{-}\overset{-}{Al}Cl_3 + AlOCl$$

utilizing two moles of catalyst in the process. Ultimately it can form a small amount of the other ketone, as long as any unreacted aromatic component remains available. When only two moles of catalyst are employed, diversion of a portion of it to these secondary steps may deplete the available supply enough to cause incompleteness, or partial reversal, of the initial coördination of catalyst with anhydride; this might explain the changes in yields and ratios of the ketones when catalyst quantities were reduced.

As evidence that such behavior is not peculiar to one small group of mixed aliphatic anhydrides, we may refer again to Kammann's collateral work,[12] citing pertinent data on the Friedel–Crafts acylation of benzene with benzoic *p*-nitrobenzoic anhydride, and with an equimolar mixture of the two corresponding acyl halides. Excess benzene was used as a solvent, and times and temperatures were not identical to those of the present work, but the procedures were fundamentally similar. The mole per cents of the two ketonic products obtained were as follows: from the mixed anhydride: benzophenone, 84.5, and *p*-nitrobenzophenone, 15.5; from the mixture of two acyl halides: benzophenone, 53.9, and *p*-nitrobenzophenone, 46.1. Although reversal of predominance was not quite achieved here, the trend in that direction is marked.

Formic acetic anhydride has been found previously to be an effective formylating agent in esterification and in amide formation[3,16]; if it could be made to play a similar role in a Friedel–Crafts reaction, this would offer a new way of preparing aromatic aldehydes. A paper[17] which appeared while the present work was in progress contained a brief statement of its authors' failure to obtain aldehydes in this manner, but did not indicate the scope or the conditions of their experiments. We explored this possibility with benzene, toluene, naphthalene, thiophene, and furan, under a variety of conditions, using catalysts appropriate to the aromatic components, but no convincing evidence of aldehyde formation could be obtained. In two isolated experiments, one with naphthalene and the other with furan, faint qualitative indications of aldehydes were observed; but attempts to corroborate these by other tests, and to reproduce them, were unsuccessful. Under the conditions of this study, the only carbonyl derivatives definitely obtained from formic acetic anhydride were methyl ketones, usually in mediocre yields.

Experimental

Mixed Acetic Anhydrides.—Formic acetic anhydride was prepared from formic acid and acetic anhydride.[16a]

All other mixed anhydrides were made from ketene and the appropriate carboxylic acids, as described originally by Hurd and Dull,[2] with minor modifications, using a small excess of ketene. The crude anhydrides were subjected to suction to remove volatile contaminants, washed quickly with cold 10% aqueous sodium carbonate, dried over calcium chloride, and again subjected to suction. The washing was omitted with formic acetic and acetic chloracetic anhydrides. To minimize disproportionation, all materials were maintained at 0–5° throughout the above-described procedure, and all steps (including commencement of the subsequent Friedel–Crafts reactions) were expedited as much as possible. The mixed acetic anhydrides of caproic, heptanoic, octanoic, α-methylbutyric, and β-methylbutyric acids were used without fractional distillation; formic acetic anhydride was always distilled; the others were distilled just before use in some runs, and used undistilled in others. Neutralization equivalents and refractive indices were determined for every batch, and samples of one or more batches of each anhydride except formic acetic were subjected to elemental analysis. Data describing a typical example of each one are shown in Table V.

With the exception of formic acetic and acetic chloracetic anhydrides, none of these mixed anhydrides effervesced actively when shaken with cold aqueous sodium carbonate, showing that there had been no substantial disproportionation, since most simple anhydrides (and specifically acetic anhydride) react rapidly with such solutions, with copious evolution of carbon dioxide. Occasional tests with similar sodium carbonate solutions were made on samples withdrawn from the mixed anhy-

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[15] *Cf.* (a) J. V. Heid and R. Levine, *J. Org. Chem.*, **13**, 409 (1948); (b) D. P. N. Satchell, *J. Chem. Soc.*, 1899 (1962).

[16] (a) A. Behal, *Compt. rend.*, **128**, 1460 (1899); (b) W. R. Edwards, Jr., and L. H. Reeves, *J. Am. Chem. Soc.*, **64**, 1583 (1942); (c) C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958); (d) *Cf.* also P. H. Groggins, R. H. Nagel, and A. J. Stirton, *Ind. Eng. Chem.*, **26**, 1317 (1934) for mention of an aldehyde yield of 1–2% from a Friedel–Crafts reaction, using formic acid.

[17] G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **82**, 2380 (1960).

TABLE V

QUALITIES OF MIXED ANHYDRIDES (ONE EXAMPLE OF EACH ANHYDRIDE)

Mixed acetic anhydride	Yield, %	B.p.,[a] °C. (mm.)	n^{20}_D	Neut. equiv.		Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Propionic	54	39–40 (10)	1.3969	58.1	58.1	51.72	52.01	6.95	7.02
Butyric	41	40–42 (5)	1.4043	65.1	65.1	55.37	55.07	7.75	7.60
Valeric	51	56–59 (6)	1.4092	72.1	72.3	58.31	58.47	8.39	8.24
Caproic	53	...	1.4145	79.1	80.7	60.74	60.72	8.92	8.78
Heptanoic	62	...	1.4186	86.1	87.8	62.76	62.92	9.36	9.35
Octanoic	48	...	1.4233	93.1	92.8	64.48	64.76	9.74	9.65
Isobutyric	58	38.5–40.5 (7)	1.3991	65.1	66.3	55.37	55.31	7.75	7.82
α-Methylbutyric	77	...	1.4063	72.1	74.7	58.31	58.28	8.39	8.25
β-Methylbutyric	52	...	1.4055	72.1	72.5	58.31	57.83	8.39	8.07
Chloracetic[b]	62	27–30 (0.01)	1.4280[d]	68.3	67.4	35.18	37.10	3.69	4.22
Chloracetic[c]	71	...	1.4301[d]	68.3	70.3	35.18	35.16	3.69	4.52

[a] Where no boiling point is shown, anhydride was not distilled. [b] Chlorine, %: calcd., 25.97; found, 23.89. [c] Chlorine, %: calcd., 25.97; found, 25.45. [d] Refractive indices of both samples of acetic chloracetic anhydride were measured at 25°.

drides at the start of some of the Friedel–Crafts reactions; these also, gave almost no effervescence.[18]

Comparisons of fractionally distilled mixed acetic anhydrides with undistilled ones, based on compositions, neutralization equivalents, behavior with cold aqueous sodium carbonate, and temperature ranges during distillation, led to the opinion that some net advantage was probably gained by fractionation of the formic, propionic, butyric, and isobutyric members of the series, which distilled over narrow ranges. The advantage was doubtful when the higher acyl group contained five carbons; when it had six or more, distillation appeared to be disadvantageous. In some borderline cases, ketone ratios from undistilled anhydrides were nearly the same as from distilled ones. Acetic chloroacetic anhydride presented a special problem. Since it could not be washed, there was more reason to distil it. Analytical results on it were poor, however, distilled or undistilled, and it must be assumed that it was relatively impure.

Two types of columns were used for fractional distillations of ketones and anhydrides. The usual one was a Vigreux-type vacuum-jacketed column of appropriate size. This was occasionally replaced by a 17-cm. heated column, packed with glass rings, with a total condensation variable take-off still head.

Friedel–Crafts Acylation of Benzene.—Benzene, anhydride, and aluminum chloride were used in a molar ratio of 1:1:3, except where otherwise stated, the actual weight of catalyst being 4 g. in excess of the quantity called for by the ratio. The usual quantity of anhydride was a little under 0.2 mole. The reaction vessel, containing 200 ml. of carbon disulfide and the catalyst, was cooled to 0°, with stirring which continued throughout the reaction. Precooled anhydride was added dropwise. With this mixture at 0°, benzene was added dropwise, 0.5 ml./min., maintaining a temperature of 0–5° during and after the addition. Total reaction time was 3 hr., measured from the first drop of benzene, except where otherwise stated. At the end of 3 hr., the reaction mixture was added cautiously to sufficient ice and hydrochloric acid to dissolve aluminum compounds. The aqueous and the organic layers were separated, and the former was extracted with three 100-ml. portions of ether, extracts being added to the organic phase. The latter, which had a total volume of about 500 ml., was washed with water, then with successive small portions of 10% aqueous sodium hydroxide until the washings were alkaline, then with water again; the total volume of these aqueous washes averaging about 180 ml. It was then dried over calcium chloride. Low-boiling components (ether, benzene, and carbon disulfide) were distilled.

The remaining material in each run consisted principally of a mixture of acetophenone and a higher ketone. The molar ratio of these was determined by gas chromatography of a sample, or by fractional distillation and weighing, or by a combination of both procedures. Distillation alone was used when the higher ketone was chloracetophenone, caprophenone, or a larger one. Gas chromatography, or a combination of both methods of estimation, was employed in most runs in which the higher ketone was of relatively low molecular weight, not differing widely from acetophenone in boiling point. Whenever distillation was used, the small intermediate fraction was further tested, either by gas chromatography or by subjecting it to an iodoform reaction, and corrections (always very slight) were made on the basis of these tests. Validities of the chromatographic measurements were established by means of similar runs made with mixtures containing known quantities of the same materials.

The identity of each ketone was established by a combination of two or more of the following: boiling point, refractive index, melting points of one or more crystalline derivatives (at least one of these for each ketone), and comparison with a known sample in the gas chromatograph.

Acylations with mixtures of two simple anhydrides, and with mixtures of two acyl halides, were performed in a manner matching the procedure described above as closely as possible. Two or more reasonably agreeing runs were made with each mixed anhydride, with each pair of simple anhydrides or acyl halides, and under each special set of conditions; data in Tables I–IV are averages of these. Additional runs were made whenever it seemed advisable, for any reason, in order to validate these data, the extreme example being a series of five runs on which were based the figures for α-methylbutyric anhydride, which displayed unusual irregularity. Results of any run in which total ketone yield was abnormally low were discarded.

Friedel–Crafts Reactions with Formic Acetic Anhydride.—Formic acetic anhydride was used with the following combinations of aromatic compound and catalyst: benzene and aluminum chloride; naphthalene and aluminum chloride; toluene and either aluminum chloride or aluminum bromide, sometimes supplemented by cuprous chloride; thiophene and either stannic chloride or zinc chloride; and furan and zinc chloride. A number of variations were made, in individual runs, in such conditions as solvent, temperature, time, catalyst quantity, proportions of reagents, and sequence of addition. In every instance, copious quantities of a gas, partially identified as carbon monoxide, were evolved throughout the reaction; in those runs in which it was determined, very little anhydride remained unchanged. Search for aldehydes in the products was made by a number of methods: attempted recovery, either directly or in the form of derivatives; qualitative tests with various reagents, including, in some cases, the specific N,N-dimethyl-*p*-phenylenediamine[19]; in some runs, either infrared spectrophotometric examination, or column chromatography. Results of this search were negative, with the possible exception of slight and inconclusive indications of traces

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(18) *Cf.* L. Brown and I. F. Trotter, *J. Chem. Soc.*, 87 (1951), describing infrared study of the equilibrium between acetic butyric anhydride and the two simple anhydrides, from which it may be inferred that with the low temperatures and short elapsed times of the present work, disproportionation of acetic butyric anhydride was insignificant.

(19) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta.*, **37**, 1901 (1954).

of aldehydes in one run with naphthalene, and one with furan. In neither of these two cases could the presence of an aldehyde be corroborated by other tests, and when the runs were repeated the positive indications failed to reappear.

Acknowledgment.—The authors are grateful for a research grant from the Esso Standard Oil Company, Baton Rouge, Louisiana. They also acknowledge their indebtedness to V. F. Farrugia, who contributed useful empirical information on the preparation and use of mixed anhydrides, and who also performed part of the work with formic acetic anhydride which is summarized here.

The Stereochemistry of the Nucleophilic Addition of *p*-Toluenethiol to 1-*p*-Tolylsulfonylcyclopentene[1]

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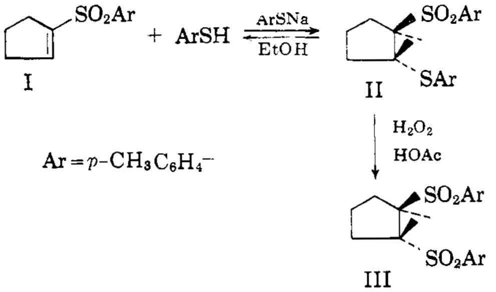
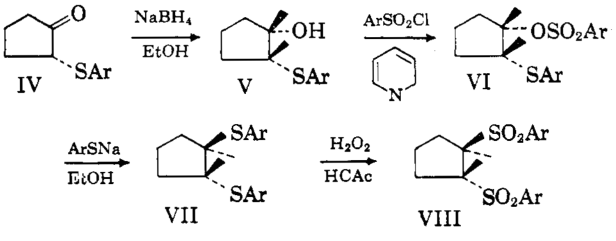
Received August 10, 1962

Under mildly basic conditions *p*-toluenethiol adds to 1-*p*-tolylsulfonylcyclopentene to give *trans*-2-*p*-tolymercapto-1-*p*-tolylsulfonylcyclopentane. The stereochemistry of the adduct was proved by an independent synthesis. An explanation, together with supporting evidence, for the stereoselectivity involved is given.

Having demonstrated[2] that *p*-toluenethiol adds to 1-*p*-tolylsulfonylcyclohexene under mildly basic conditions to give, *via* a *trans* addition, *cis*-2-*p*-tolylmercapto-1-*p*-tolylsulfonylcyclohexane, it was decided to study the stereochemistry of like additions to other activated cyclic olefins. Accordingly, *p*-toluenethiol was added to 1-*p*-tolylsulfonylcyclopentene (I)[3] in the presence of a 0.1 molar equivalent of sodium ethoxide in ethanol. The resulting adduct (II) was oxidized to its respective disulfone (III).

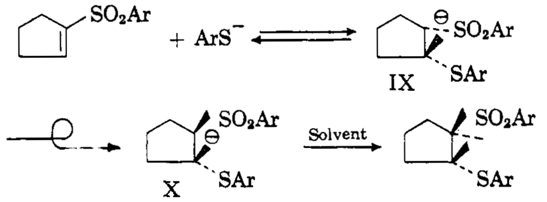


trans-1,2-Bis-*p*-tolylsulfonylcyclopentane was independently synthesized in the following manner:



Reduction of the keto sulfide (IV) by sodium borohydride in ethanol gave the *cis*-hydroxy sulfide (V) which was converted to its tosylate (VI). The tosylate was shown to have a *cis* configuration by demonstrating that it could be oxidized to the known[3] *cis*-2-(*p*-tolylsulfonyl)cyclopentyl *p*-toluenesulfonate. The S_N2 displacement by thiolate upon *cis*-2-(*p*-tolylmercapto)cyclopentyl *p*-toluenesulfonate (VI) would be expected to lead to inversion even if the unlikely possibilities of isomerization or anchimeric assistance are taken into consideration. Elimination of *p*-toluenesulfonic acid from VI followed by addition of thiolate to the resulting vinyl sulfide to give a dithioether with a *cis* configuration was discredited by a demonstration that thiolate does not add to vinyl sulfides under these reaction conditions. The independently prepared *trans*-disulfone (VIII) was shown to be identical to III. Thus III and therefore the adduct (II) have a *trans* configuration.[4]

These *over-all* results are opposite to those in the cyclohexyl system in which an adduct of *cis* configuration is obtained under identical conditions. This difference can be explained by greater steric strain in the *cis*-cyclopentyl system relative to the *cis*-cyclohexyl system. The addition is presumed to proceed through the following mechanistic path:



Presumably there is more steric strain in the anion intermediate (IX) due to interaction between an arylsulfonyl group and an arylmercapto group than in the corresponding *cis*-cyclohexyl anion (XI), in which the

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[1] Abstracted from the Ph.D. thesis of A. J. Levy, Purdue University, 1962.

[2] W. E. Truce and A. J. Levy, *J. Am. Chem. Soc.*, **83**, 4641 (1961).

[3] F. G. Bordwell and R. J. Kern, *ibid.*, **77**, 1141 (1951).

[4] An attempt was made to prepare *trans*-2-(*p*-tolylmercapto)cyclopentyl *p*-toluenesulfonate (from its respective alcohol, *p*-toluenesulfonyl chloride and pyridine) as an intermediate toward the preparation of *cis*-1,2-bis-*p*-tolylmercaptocyclopentane. The only products isolated, however, were pyridinium *p*-toluenesulfonate and *trans*-2-*p*-tolylmercapto-1-chlorocyclopentane. This reaction is an excellent example of neighboring group participation by bivalent sulfur.