isoquinoline. A. For 24 hr.—The amine X (389 mg, 1 mmole) was added, in small portions, to a solution of lithium aluminum hydride (380 mg, 10 mmoles) in tetrahydrofuran. Addition was effected at such a rate that the tetrahydrofuran refluxed. Heating at reflux was continued for 24 hr, after which the reaction mixture was cooled to room temperature and the remaining lithium aluminum hydride was destroyed by addition of water. The resulting suspension was made strongly alkaline with 10% sodium hydroxide and continuously extracted with ether. Chromatography of the extract on alumina (Woelm III, neutral) gave, with 1:1 chloroform–benzene eluent, crystalline amine X (204 mg, 53% recovery); on elution with chloroform–methanol (99:1) 1-(*o*-aminobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (II, 51 mg, 13%), identical with that prepared by the reduction[6] of 1-(*o*-nitrobenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline with zinc and hydrochloric acid, was removed.

B. For 4 days.—The above reaction was repeated on the same scale and the reaction mixture was refluxed for 4 days. Chromatography of the resultant products yielded, after crystallization from methanol (chloroform–benzene eluent, 1:1), 20.3 mg (5.23%) of white crystals of diamine VII, mp 137–138°. The analytical sample, mp 141–142°, was obtained by recrystallization from methanol.

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.50; N, 7.52. Found: C, 77.11; H, 6.65; N, 7.33.

Continued elution of the column with chloroform–methanol (99:1) yielded diamine II (258 mg, 68%).

1-(*o*-Nitrobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (XII).—A solution of nitroamide IX (500 mg, 1.20 mmoles) in dry tetrahydrofuran (30 ml) was added dropwise (nitrogen atmosphere) with stirring during 10 min to a cooled solution (ice bath) of diborane in tetrahydrofuran (15 ml, 15 mmoles).[12] When the addition was complete, the solution was allowed to warm to room temperature and was then refluxed for 12 hr. After cooling to room temperature, 6 *N* hydrochloric acid (50 ml) was added cautiously. The reaction mixture was warmed on the steam bath until evolution of hydrogen ceased and the solvent was removed *in vacuo*. The solid residue was suspended in chloroform and shaken with dilute sodium hydroxide solution (10%) until all of the solid had dissolved. The aqueous phase was washed with fresh chloroform and the combined chloroform extracts were washed with water and evaporated to dryness. Crystals of nitroamine XII (424 mg, 87.5%), mp 82–83°, were obtained from methanol–chloroform.

Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 72.36; H, 5.50; N, 6.70.

1-(*o*-Aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VII).—1-(*o*-Nitrobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (XII, 4.05 g, 1 mmole) was suspended in methanol (500 ml) and 10% palladium on carbon (2.5 g) was added (nitrogen atmosphere). Hydrazine hydrate (2 ml of 85%, diluted to 8 ml with methanol, 8 mmoles) was added dropwise to the stirred and refluxing mixture, and refluxing was continued overnight. The warm solution was filtered through a thin Celite mat and evaporation of the filtrate afforded 3.26 g (86.6%) of VII as white needles, mp 141–142°. The product was identical with that (melting point, mixture melting point, and infrared spectrum) produced in low yield from X through the action of lithium aluminum hydride. Continuous extraction of the catalyst in a Soxhlet apparatus yielded an additional 63 mg of oil which could not be induced to crystallize. Treatment of a methanolic solution of the oil with 6 *N* hydrochloric acid yielded needles, mp 238–240°, identical with authentic 1-(*o*-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline hydrochloride by melting point, mixture melting point, and infrared spectrum.

N-Benzyl-*dl*-anonaine (III).—1-(*o*-Aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VII, 1.33 g, 3 mmoles) was dissolved in a mixture of glacial acetic acid (10 ml) and concentrated sulfuric acid (1 ml) and the clear, colorless solution was cooled to 10°. A solution of sodium nitrite (221.6 mg, 3.19 mmoles) in water (2 ml) was added dropwise for several minutes The resulting bright orange solution was stirred at 10° for an additional 15 min and a few crystals of sulfamic acid were then added, followed by acetone (50 ml), cuprous chloride (50 mg), and freshly prepared metallic copper (2 g). Nitrogen was evolved vigorously from the stirred solution for several minutes, after which it was warmed on the steam bath and then refluxed for 30 min. The acetone was removed by distillation and the residual suspension was cooled to room temperature and then made basic with ammonium hydroxide. The blue aqueous solution was continuously extracted with ether for 24 hr and the ethereal extract was evaporated to dryness. The residue was chromatographed on a 1 in. × 10 in. column of Woelm grade I neutral alumina. Elution with benzene afforded 1-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline: mp 102–104°; λ_{max} 214 mμ (log ϵ 4.52), 295 (4.02).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.30; N, 3.92.

Further elution with benzene afforded N-benzyl-*dl*-anonaine (crystals from chloroform–methanol, 332 mg, 31%): mp 129° and second mp 146°; λ_{max} 211 mμ (log ϵ 4.48), 270 (4.13), 318 (3.49).

Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.70; H, 6.00; N, 3.66.

***dl*-Anonaine (I).**—N-Benzyl-*dl*-anonaine (III, 826.9 mg, 2.32 mmoles) was placed in a Parr bottle together with 10% palladium on carbon (1.0 g), concentrated hydrochloric acid (5 ml), and ethyl alcohol (95%, 100 ml). Hydrogenolysis was carried out at 49 psi for 24 hr. The catalyst was removed by filtration and was extracted with ethanol in a Soxhlet apparatus. The extract was combined with the filtrate and evaporated to dryness to yield 690 mg (97%) of crystalline *dl*-anonaine hydrochloride, mp 285° dec (lit.[2b] mp 295°).

Anal. Calcd for $C_{17}H_{10}NO_2$: C, 67.66; H, 5.31; N, 4.66. Found: C, 67.68; H, 5.48; N, 4.56.

Neutralization of the above hydrochloride afforded *dl*-anonaine, which crystallized readily (ether) as small prisms, mp 114.5–115° (lit.[2b] mp 116.5°).

Liriodenine (XIII).—*dl*-Anonaine (I, 47.5 mg, 0.127 mmole) was dissolved in *t*-butyl alcohol (25 ml) and filtered air was passed through the solution for a period of 5 days. At the end of this time, the solution was evaporated to dryness *in vacuo*. The residue, in chloroform solution, was transferred to neutral alumina preparative chromatography plates. The plates were developed with chloroform and liriodenine was recovered from the bright yellow band (R_f 0.32) by extraction of the stationary phase with methanol–chloroform (1:10). The sample (14.7 mg, 31%), mp 275–280° dec, was identical (melting point, mixture melting point, and infrared spectrum) with an authentic sample from natural sources.[14]

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(14) This material was kindly supplied by Professor J. Beal, College of Pharmacy, The Ohio State University.

Friedel–Crafts Acylation of Thiophene with Mixed Acetic Anhydrides[1a]

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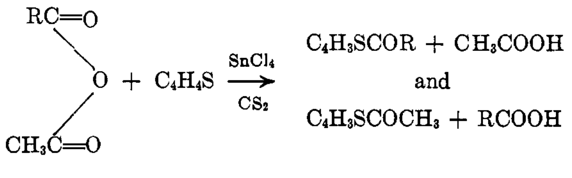
An earlier paper[2] described the behavior of a number of mixed acetic anhydrides, when these reacted with limited quantities of benzene in the presence of aluminum chloride, and gave particular attention to the molar ratios of the two possible ketonic products. The relative ketone-forming proficiencies of the competing acyl groups appeared to be influenced substantially by their electronic qualities, and to a lesser extent by their steric characteristics. Marked dif-

(1)(a) From the M.S. Thesis of Robert J. Eckert, Jr., Louisiana State University, June 1962. (b) Cities Service Honor Fellow, 1961–1962.

(2) W. R. Edwards, Jr., and E. C. Sibille, *J. Org. Chem.*, **28**, 674 (1963).

ferences were observed between the ketone ratios obtained with certain mixed anhydrides and those obtained by using equimolar mixtures of either the two corresponding acyl chlorides or the two simple anhydrides.

To confirm and extend that earlier work, and to broaden the foundation for inferences drawn from it, we have studied the actions of seven mixed acetic anhydrides, under essentially similar conditions, on the more nucleophilic thiophene, using stannic chloride as catalyst. The two competing reactions in the present work are shown below. In both studies, the aromatic or heterocyclic substrate was added slowly to a mixture containing an equimolar quantity of the anhydride, the catalyst, and the solvent (Perrier procedure), in order to minimize secondary reactions by avoiding the presence of excess substrate at any stage of the process; disproportionation of the mixed anhydride was discouraged by utilizing it promptly, and by maintaining constant low temperature.



The results are shown in Table I. The right-hand column contains a relevant portion of the data from the earlier work with six of the same anhydrides, inserted here for comparison. Qualitatively, the present results paralleled the earlier ones and were in harmony with most of the observations offered in the previous paper, though there were indications that the relative importance of the steric factor was greater than in the reactions with benzene and aluminum chloride. In the absence of branching at its α carbon, the higher ketone predominated in every instance, in both series, but not to an extent related directly to chain length or total size. The mole per cent of each higher thienone, however, was smaller than that of the corresponding phenone. In both series, α branching depressed the formation of the higher ketones substantially. This depression was more pronounced in the thienones, where, in conjunction with the general tendency of the mole per cents of higher thienones to fall below those of higher phenones, it was sufficient to cause small biases in favor of 2-acetothienone over 2-isobutyrothienone and 2-α-methylbutyrothienone. The influence of such branching was accentuated by the sharp predominance of acetothienone in the products of the reaction with acetic pivalic anhydride, an acylating agent which was not employed in the work with benzene.

TABLE I

ACYLATIONS WITH MIXED ACETIC ANHYDRIDES[a]

Mixed acetic anhydride	Approx total ketone yield, %[b]	Mole % of each ketone in total carbonyl product: 2-Acetothienone	Higher thienone	Mole % of higher phenone in comparable acylations of benzene[c]
Butyric	77.0	38.7	61.3	72.9
Valeric	68.2	38.9	61.1	80.1
Heptanoic	60.1	34.9	65.1	75.1
Isobutyric	67.7	55.2	44.8	60.9
Isovaleric	72.7	41.1	58.9	80.7
α-Methylbutyric	67.0	53.8	46.2	69.8
Pivalic	76.4	90.6	9.4	...

[a] Except in right-hand column, aromatic component was thiophene; catalyst was $SnCl_4$; molar ratio of thiophene:anhydride:catalyst was 1:1:3.15; reaction temperature was 0–5°; reaction time was 5 hr. [b] Based on weight of thiophene. [c] Data in this column were taken from ref 2. Aromatic component was benzene; catalyst was $AlCl_3$; reaction time was 3 hr; other conditions were like those of the present work.

At this time we are unable to say how responsibility for the quantitative differences between the two series should be divided between the electronic and steric qualities of the substrates and those of the catalysts, respectively. Attempts to throw light on this question, by means of experiments in which substrates and catalysts were interchanged, were unsuccessful. With benzene, stannic chloride, and acetic butyric anhydride, no ketones were observed after 5 hr at 0°. With thiophene, aluminum chloride, and the same anhydride, tar formation was so great that the results were meaningless.

Table II contains data secured by parallel acylations of thiophene with (1) a mixed anhydride, (2) an equimolar mixture of the two corresponding simple anhydrides, and (3) an equimolar mixture of the two acyl chlorides. Comparable conditions were established by using reagents and catalyst in the indicated proportions, and by making all other conditions uniform. The right-hand column shows a portion of the data from analogous earlier work with benzene and aluminum chloride.

In both sets of experiments (and also in two other sets described in the earlier paper) the mole per cents of the higher ketones dropped moderately when the acylating agent was changed from mixed anhydride to a mixture of simple anhydrides. They dropped so substantially when a mixture of acyl chlorides was used, that their predominances were either reversed or nearly eliminated. In all of the acylations performed with acyl chloride mixtures, molar ratios of the ketonic products were never far from 1:1, in contrast to the pronounced biases which appeared whenever the acylating agent was a mixed anhydride. Although there were quantitative differences, this general pattern of behavior was not altered by the shift from benzene and aluminum chloride to the more nucleophilic thiophene and the less active stannic chloride.

The data in Table II lend support to the previously expressed idea[2–4] that Friedel–Crafts acylation with carboxylic anhydrides and Lewis acid halide catalysts does not necessarily proceed to any major extent through the preliminary formation of acyl halides, as proposed by Groggins and Nagel[5] and commonly accepted.[6] Here, as in the earlier work, the results seem more compatible with the alternate possibility of coordination of the entire anhydride molecule, through one of its carbonyl oxygen atoms, with the catalyst, followed by nucleophilic attack on this complex by the substrate. If a mechanism such as this prevails, then, whenever a mixed anhydride is used, the electronic and steric qualities of its competing halves

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[3] J. V. Heid and R. Levine, *J. Org. Chem.*, **13**, 409 (1948).

[4] D. P. N. Satchell, *J. Chem. Soc.*, 1899 (1962).

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

[6] P. H. Gore, "Friedel-Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 16, 32.

TABLE II

COMPARISONS OF ACYLATIONS WITH MIXED ANHYDRIDE, EQUIMOLAR MIXTURE OF SIMPLE ANHYDRIDES, AND EQUIMOLAR MIXTURE OF ACYL CHLORIDES[a]

Acylating agent(s)	Molar proportions of acylating agent(s): thiophene:$SnCl_4$	Approx total ketone yield, %	Mole % of each thienone		Mole % of higher phenone in comparable acylations of benzene[b]
			Acetothienone	Higher thienone	
Acetic butyric anhydride	1:1:3.15	77.0	38.7	61.3	72.9
Acetic anhydride and butyric anhydride	(0.5 + 0.5):1:3.15	69.2	42.6	57.4	63.6
Acetyl chloride and butyryl chloride	(1 + 1):1:2.10	61.1	52.9	47.1	43.7

[a] Except in the right-hand column, aromatic component was thiophene; catalyst was $SnCl_4$; reaction temperature was 0–5°; reaction time was 5 hr. [b] Data in this column were taken from ref 2. Aromatic component was benzene; catalyst was $AlCl_3$; reaction time was 3 hr; other conditions were similar to those of the present work.

should determine the ratio of the ultimate ketones by their influences on (a) the relative rates of formation of the two possible complexes of anhydride and catalyst, and (b) the relative rates of the subsequent nucleophilic displacements of these complexes.

Experimental Section

Mixed acetic anhydrides were prepared from ketene and the appropriate carboxylic acids, without solvent, following the earlier procedure,[2,7] with minor modifications, for all except acetic pivalic anhydride. They were not distilled. Their authenticities were verified in every run by determinations of their neutralization constants and by comparisons of their refractive indices with previously reported values.

Pivalic acid, a solid, was warmed slightly above its melting point (35.5°) and ketenized in the molten state for 5–10 min. Ketenization was then completed at 0–5°, the reaction mixture remaining liquid, after which the product was treated like the other anhydrides. A typical preparation, using 35.0 g of pivalic acid, gave 21.8 g (44.1%) of acetic pivalic anhydride: $n^{20}D$ 1.4027 (not previously reported); neut equiv, 73.1 (calcd, 72.1).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.48; H, 8.61.

Acylations of Thiophene.—Essentially, the procedure paralleled the acylations of benzene described in the earlier paper,[2] up to the point at which the molar ratios of the products were determined. In most runs, the quantity of the mixed anhydride was 0.12–0.17 mole, and the dropwise addition of the equimolar amount of thiophene required about 30 min. Total reaction time, from the first drop of thiophene to the ultimate quenching with ice and hydrochloric acid, was 5 hr; this gave total ketone yields approximating those achieved in 3 hr, with benzene and aluminum chloride, in the earlier work.

After washing and drying the reaction products and removing carbon disulfide, ether, and any unreacted thiophene by distillation, the relative proportions of acetothienone and the higher thienone in the residual liquid were determined by gas chromatography. For this purpose, a Beckman GC-2 gas chromatograph was employed, with, in most cases, a 6-ft 20% silicone SF 96 on 30–60 Silocel column. Calibration was achieved and validities were established by comparable measurements of mixtures containing known amounts of the same materials; general accuracy was within 0.5 mole %.

To obtain some measure of the yields of the two thienones, the residual liquid was then distilled under reduced pressure, using a vacuum jacketed Vigreux column 7 cm high and 1.5 cm in diameter, and the distillate boiling over a range which spanned their two boiling points was collected. This fraction was regarded as a crude mixture containing practically all of both ketones and no significant quantity of any other substance, and the approximate yields were calculated from its weight and from the chromatographically determined relative proportions. Pure samples of the thienones (with the exception of pivalothienone) were then obtained from these mixtures by repeated fractional distillations, using a vacuum jacketed column 20 cm high and 1.5 cm in diameter, packed with glass pearls or stainless steel helices. Their identities were established by comparisons of their chromatographic retention times, infrared spectra, and refractive indices, and the melting points of their crystalline derivatives with those of authentic samples of the same compounds or with values reported in the literature.

Because of the small quantity formed, pivalothienone was not isolated in a pure state. Its chromatographic retention time was identical with that of a reference specimen, prepared from pivalyl chloride, thiophene, and stannic chloride, at 0°; the infrared spectrum of the residue, after removal of acetothienone from the reaction products by distillation, showed all of the significant bands of the reference material. This residue, treated with 2,4-dinitrophenylhydrazine, gave a small amount of a yellow solid, mp 172.5–173.5° after recrystallization from ethanol. From the reference material there was obtained a 2,4-dinitrophenylhydrazone, mp 173–174°; a mixture of the two also melted at 173–174°.[8]

Anal. (reference hydrazone). Calcd for $C_{15}H_{16}O_4N_4S$: N, 16.09; S, 9.20. Found: N, 16.30; S, 9.40.

The acylations with the simple anhydride mixture and with the acyl chloride mixture (Table II) were preformed as nearly as possible in the same manner as those with the mixed anhydrides. To minimize any interaction between them, leading to formation of the mixed anhydride,[9] the two simple anhydrides were cooled separately and combined at the last moment.

The data in both tables are averages of the values obtained in three reasonably agreeing runs made with each mixed anhydride and with each mixture of simple anhydrides or acyl chlorides. Results were discarded in any run in which total thienone yield was abnormally low.

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

[8] Melting points were determined on a Fisher-Johns melting point block and are uncorrected.

[9] See L. Brown and I. F. Trotter, *J. Chem. Soc.*, 87 (1951), for a study of the equilibrium between acetic butyric anhydride and the two simple anhydrides.

Some Observations on the Steroid Ring-D-Fission C-Aromatization Reaction

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Cross, Carpio, and Crabbé[1] have described an unusual reaction of estrone methyl ether with chloranil: treatment of the reactants in a refluxing mixture of dioxane and *t*-butyl alcohol for 40 hr gave, in addition to the expected 9,11-dehydro compound, a by-product which proved to be the substituted dihydrophenanthrene I (R = *t*-Bu). We also encountered this reaction in a somewhat different system which is noteworthy

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[1] A. D. Cross, H. Carpio, and P. Crabbé, *J. Chem. Soc.*, 5539 (1963).