μ). Similarly XII, m.p. 114–116°, was obtained in 80% yield. Recrystallization of XII from methanol afforded the analytical sample, m.p. 117–118° (infrared band at 5.92 μ). Small amounts of the acids, V and XI, were received from alkaline extracts of the reaction mixtures.

Anal. Calcd. for $C_{20}H_{17}FO$: C, 82.2; H, 5.9; F, 6.5. Found for VII: C, 81.9; H, 6.0; F, 6.5. Found for XII: C, 82.2; H, 5.9; F, 6.4.

5-Fluoro-9,10-dimethyl-1,2-benzanthracene (IX) and 8-Fluoro-9,10-dimethyl-1,2-benzanthracene (XIII).—A solution of 1.5 g. of VI in 50 ml. of benzene was treated with a solution of methyllithium made from 1.0 g. of lithium and 10 g. of methyl iodide in 150 ml. of ether. After refluxing overnight the mixture was worked up to yield crude IX which purified by chromatography over alumina (as above) to yield 174 mg. (12%) of IX, m.p. 130–131°. Alternately, in the best of several runs, 2.2 g. of VII was stirred into 50 g. of polyphosphoric acid[13] (PPA) at 85°. After 40 min. the mixture was poured on ice and left until the dark color disappeared (2–3 hr.). The yellow solid was purified by chromatography over alumina and recrystallization from ethanol to yield 0.86 g. (41%) of pure IX, m.p. 130–131°, as pale yellow plates.

In a similar way (at 80° for 40 min.), 4.2, g. of XII afforded 1.95 g. (50%) of pure XIII, m.p. 61.5–62.5, as pale yellow crystals, b.p. 35–40° on recrystallization from petroleum ether.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.6; H, 5.5; F, 6.9. Found[8] for IX: C, 87.4; H, 5.5; F, 7.1. Found for XIII: C, 87.5; H, 5.6; F, 6.8.

The TNF derivative of IX was prepared in benzene and was recrystallized from acetic acid to yield brown crystals, m.p. 177–178°. The TNF derivative of XIII was prepared in, and recrystallized from, benzene. It formed brown elongated crystals, m.p. 175–176°.

Anal. Calcd. for $C_{33}H_{20}FN_3O_7$: C, 67.3; H, 3.4; F, 3.2; N, 7.1. Found[8] for IX-TNF: C, 67.1; H, 3.3; F, 3.1; N, 7.4. Found for XIII-TNF: C, 67.3; H, 3.5; F, 3.2; N, 7.2.

5-Fluoro-1,2-benzanthracene.—In a typical experiment (repeated several times) 2.0 g. of 1-(2-methyl-3-fluorobenzoyl)-naphthalene, m.p. 49–50° (obtained from the sample of ketone previously reported[3] as a liquid), was heated in a bath from 365 to 385° during 3 hr. Distillation at 3 mm. afforded a crude product which was purified by chromatography over alumina. Colorless needles, m.p. 105–106°, were obtained in about 32% yield. This material, which vapor phase chromatography on a 9 ft. × 0.125 in. Carbowax 20M column showed to be a mixture of two compounds in a ratio of 88:12, gave satisfactory analysis for a fluorobenzanthracene.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 87.6; H, 4.7; F, 7.4.

The red TNF derivative, m.p. 223–224°, was obtained by crystallization from benzene.

Anal. Calcd. for $C_{31}H_{16}FN_3O_7$: C, 66.4; H, 2.9; F, 3.4; N, 7.5. Found: C, 66.7; H, 3.2; F, 3.6; N, 7.3.

The melting point of pure 5-fluoro-1,2-benzanthracene[4] is 150°. Our crude material (about 88% pure) could be converted into the pure substance by careful purification. However, because of the difficulties involved, this route is not a good one. Our pure compound was identical with the sample supplied by Professor Bergmann as determined by comparison of the infrared spectra and X-ray powder photographs.

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[13] Compare C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 343 (1957). We thank the Victor Chemical Co., Chicago, Ill., for a generous gift of polyphosphoric acid.

The Behavior of 3-Fluorophthalic Anhydride in Friedel–Crafts and Grignard Reactions[1]

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Condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° took place only on the 2-carbonyl group to yield a mixture of 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III). In Grignard reactions with 1-naphthyl- and 2-naphthylmagnesium bromides, both possible keto acids were formed. In the case of 2-naphthylmagnesium bromide, condensation occurred at the 1-carbonyl in preference to the 2-carbonyl group of I in the ratio of about 1.4:1, whereas with 1-naphthylmagnesium bromide condensation at each carbonyl was about the same.

In previous studies from this laboratory, the reaction of 3-substituted phthalic anhydrides in Grignard and Friedel–Crafts condensations have been described.[3,4] In summary,[4] Grignard condensations take place preferentially on the 1-carbonyl group in both 3-methyl- and 3-chlorophthalic anhydride. In the Friedel–Crafts reaction, condensation occurs on both carbonyl groups in 3-methylphthalic anhydride, but with 3-chlorophthalic anhydride, condensation is almost entirely at the 2-carbonyl group.

In this paper we report on the reactions of 3-fluorophthalic anhydride with naphthalene and with 1- and 2-naphthylmagnesium bromides. This work was undertaken not only to obtain more information about the behavior of unsymmetrical anhydrides but also to ascertain the source of an error in a previous publication.[5] The consequences of this error is discussed in the accompanying article.[6]

The Friedel–Crafts condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° gave a mixture of about 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III) as determined by fractional recrystallization of the methyl esters (compare ref. 5). In a run at 45°, II and III were produced in about 22 and 45% yields, respectively. At 125° the proportion of II increased over that in the run at 95°, but yield of acids was lower owing to tar formation. Thus in the Friedel–Crafts condensation with naphthalene, 3-fluorophthalic anhydride behaves like 3-chlorophthalic anhydride in that condensation occurs

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[1] This work was supported by a grant from The National Institutes of Health, Bethesda, Md.

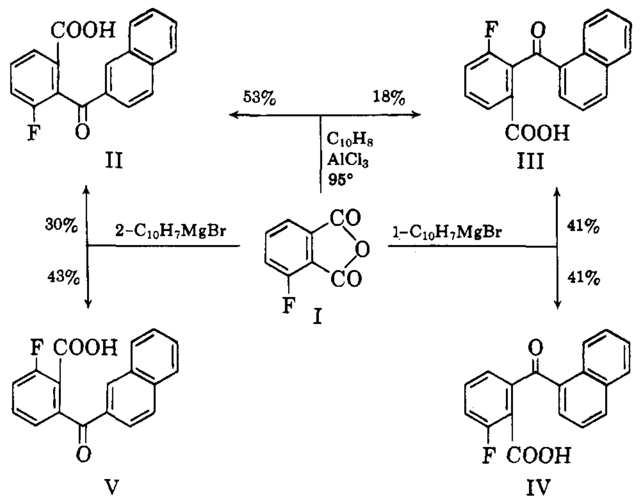
[2] Postdoctoral Fellow, 1963.

[3] (a) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); (b) M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950).

[4] M. S. Newman and P. G. Scheurer, *ibid.*, **78**, 5004 (1956).

[5] M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

[6] M. S. Newman and S. Blum, *ibid.*, **29**, 1414 (1964).



exclusively at the internal 2-carbonyl. This result does not agree with that reported previously.[5] We believe the previous report to be in error.

When a solution in ether–benzene (2:1) of the Grignard reagent from 1-bromonaphthalene was added to a solution of 3-fluorophthalic anhydride in benzene, about 84% of a mixture of crude keto acids III and IV was obtained. After several unsuccessful attempts at separation of the mixture were made (see Experimental section) an excellent analysis was made by n.m.r. The τ values of the methyl groups in the methyl esters of III and IV (made with diazomethane) were sufficiently different that n.m.r. analysis could be used to show that about equal amounts of III and IV had been formed.[7]

When 2-naphthylmagnesium bromide reacted with I under similar conditions, the acids II and V were formed in about 30 and 43% yields, respectively. The greater preference of the 2-naphthyl Grignard reagent to react at the 1-carbonyl group of I is what would be expected since a similar result was obtained with phenylmagnesium bromide with both 3-methyl- and 3-chlorophthalic anhydrides.[3,4] However, the proportion reacting at the 1-carbonyl as compared to the 2-carbonyl is not so great as in the previous cases.[3,4] The most surprising fact, however, is that 1-naphthylmagnesium bromide reacts about equally well at each carbonyl in I. We have no explanation to offer for this fact.

The structures of the keto acids II–V were proved by decarboxylation to fluorophenyl naphthyl ketones. Authentic samples were made by condensation of Grignard reagents with nitriles. Identities were established by mixture melting point determination and by infrared spectral comparisons.

Experimental[8]

3-Fluorophthalic Anhydride (I).—A slight modification of the directions for oxidation of 2,3-dimethylfluorobenzene[5] made it possible to obtain the stated yield more consistently. To a stirred mixture of 93 g. of 3-fluoro-1,2-dimethylbenzene,[9] 25 g. of potassium hydroxide, and 500 ml. of water at reflux was added 100 ml. of a boiling solution made from 600 g. of potassium permanganate in 2.5 l. of water. Heat was applied until oxidation commenced (a short induction time, 15–30 min., followed by precipitation of manganese dioxide), whereupon heating was discontinued and the addition of the remaining permanganate solution was made at such a rate as to hold the reaction under control (about 2–3 hr.). Heat was then applied (about 30 min.) until all of the water-insoluble layer had disappeared. The excess permanganate was destroyed with sodium bisulfite and the manganese dioxide was filtered and washed with boiling water. The filtrate and washings were worked up as described[5] to yield 108 g. of 3-fluorophthalic acid, m.p. 162–165°.

Distillation afforded the anhydride[5] I.

Friedel–Crafts Reactions. 3-Fluoro-2-(2-naphthoyl)benzoic Acid (II) and 3-Fluoro-2-(1-naphthoyl)benzoic Acid (III).—Powdered anhydrous aluminum chloride (74 g.) was added (*ca.* 2 hr.) in portions to a stirred solution of 41.5 g. of I and 38.5 g. of naphthalene in 500 ml. of *o*-dichlorobenzene so that the temperature remained at 95–98°. After 2 hr. more of stirring at this temperature the cooled mixture was poured on ice and worked up to yield 67 g. (91%) of light tan acid,[10] m.p. 135–141°. Separation of this mixture was effected by the following procedure. A solution of 90 g. of the above acid was refluxed in 1 l. of methanol containing much hydrogen chloride for 16 hr. The esters produced were isolated by conventional procedure and recrystallized from methanol. The more insoluble methyl ester of III ($\mathrm{III_{me}}$) was obtained in 18% yield in several crops as slightly tan crystals, m.p. 121–123°. The analytical sample,[11] m.p. 124.5–125.5°, was obtained by recrystallization from ethanol. On standing and by further concentration of certain portions of the mother liquors from the above crystallization there was obtained a total of 49.5 g. (53%) of methyl 3-fluoro-2-(2-naphthoyl)benzoate ($\mathrm{II_{me}}$), m.p. 91–94°. The analytical sample, m.p. 95–96°, was obtained with little loss on crystallization from cyclohexane.

Anal. Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.2; F, 6.2. Found[12] for $\mathrm{II_{me}}$: C, 74.2; H, 4.2; F, 6.4. Found for $\mathrm{III_{me}}$: C, 73.8; H, 4.1; F, 6.4.

On hydrolysis with alcoholic alkali, the above esters yielded II, m.p. 200.0–201.5° after recrystallization from xylene, and III, m.p. 187–188° on recrystallization from toluene, in high yields.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7; F, 6.5. Found for II: C, 73.6; H, 3.8; F, 6.7. Found for III: C, 73.5; H, 3.8; F, 6.6.

Grignard Reactions.—The Grignard reagent prepared from 21 g. of 1-bromonaphthalene in 100 ml. of ether and 50 ml. of benzene was added during 10 min. to a stirred boiling solution of 16.6 g. of I in 150 ml. of benzene. After refluxing for 6 hr. the mixture was cooled and worked up as usual to yield 24.8 g. (84%) of acids, m.p. 114–120°. A suspension of 19 g. of this acid in ether was treated with diazomethane to yield a mixture of methyl 3-fluoro-2-(1-naphthoyl)benzoate ($\mathrm{III_{me}}$) and methyl 2-fluoro-6-(1-naphthoyl)benzoate ($\mathrm{IV_{me}}$). Analysis of this mixture by n.m.r. showed that the yields of III and IV were about 41% each (average of three runs).[13]

Pure samples of $\mathrm{III_{me}}$ and $\mathrm{IV_{me}}$ were obtained as follows. In a typical experiment a solution of 5.0 g. of the mixed methyl esters of III and IV, made by treatment with diazomethane, in a

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[7] In a private communication during the course of our work, Dr. E. D. Bergmann and Dr. M. Bentov informed us that 2-fluoro-6-(1-naphthoyl)benzoic acid is formed in 63% yield when the condensation is carried out in tetrahydrofuran [see *Bull. soc. chim. France,* 963 (1963)]. This strong solvent effect is noteworthy.

[8] All melting points are uncorrected. The term "worked up in the usual manner" means that a solution of the products in an organic solvent, usually ether–benzene, was washed with acid and/or alkali as required and saturated sodium chloride solution, and then was dried by shaking with, or filtration through, anhydrous magnesium sulfate. The solvents were then removed and the residue was purified by crystallization, distillation, or chromatography.

[9] This was obtained from the Pierce Chemical Company, Rockford, Ill.

[10] In ref. 5 a melting point of 176–178° was reported for acid obtained by essentially the same procedure. However, we have never been able to repeat this result, as invariably in many runs acid, m.p. 135–141°, was obtained by Dr. S. Blum and Dr. D. Alsop.

[11] In ref. 5, this ester was reported to melt at 95–96°. However, we are certain that the ester referred to therein was methyl 3-fluoro-2-(2-naphthoyl)benzoate ($\mathrm{II_{me}}$), as an authentic sample of this ester melts at 95–96°.

[12] All analyses by Galbraith Microanalytical Laboratory, Knoxville, Tenn.

[13] The use of n.m.r. to determine the amounts of normal methyl esters of these acids was prompted by the publication by P. T. Lansbury and J. F. Bieron [*J. Org. Chem.,* **28**, 3564 (1963)] for which M. S. N. was a referee. We thank Mr. B. Bossenbroek for carrying out the spectral determinations. The value for the methyl group in $\mathrm{III_{me}}$ was 6.46 and in $\mathrm{IV_{me}}$ was 6.50.

TABLE I

PREPARATION OF KETONES AND DNPH DERIVATIVES

Keto acid	Ketone[a]	Yield,[b] %	M.p.,[c] °C.	Anal.,[d] %			DNPH, m.p. dec., °C.	Color	Anal.,[e] %			
				C	H	F			C	H	F	N
II	o-FC_6H_4-2-$C_{10}H_7$–	26	81.0–82.0	81.3	4.6	7.5	300–302	Orange	64.1	3.5	4.7	12.8
III	o-FC_6H_4-1-$C_{10}H_7$–	25	58.5–60.0	81.8	4.6	7.6	283–285	Orange	64.1	3.7	4.6	12.9
IV	1-$C_{10}H_7$-m-FC_6H_4–	50	60.2–61.0	81.8	4.2	7.6	220–222	Yellow[f]	64.0	3.8	4.4	13.0
							258–260	Orange[f]	64.4	3.8	4.5	12.8
V	2-$C_{10}H_7$-m-FC_6H_4–	81	122.5–123.0	81.6	4.7	7.5	248–250	Deep yellow[g]	64.4	3.5	4.7	13.0
							283–285	Orange[g]	64.5	3.7	4.6	12.8

[a] The group used as nitrile in the synthesis is listed first and the group used as Grignard reagent, second. [b] Yield of pure ketone in Grignard reaction. [c] M.p. of pure ketone. [d] Calcd. for $C_{17}H_{11}FO$: C, 81.6; H, 4.4; F, 7.6. [e] Calcd. for $C_{23}H_{15}FN_4O_4$: C, 64.2; H, 3.5; F, 4.4; N, 13.0. [f] The mixture of DNPH derivatives was recrystallized from xylene and washed on the funnel with diglyme (dimethyl ether of diethylene glycol); the yellow form dissolved while the orange form remained. [g] Separated by recrystallization from acetic acid; the orange isomer was the more insoluble.

solution of 5.0 g. of 30% oleum and 49 g. of 98% sulfuric acid was held at 20–25° for 4 hr. The mixture was poured onto ice and separated into acid and neutral fractions by treatment with sodium carbonate.[14] There was obtained 2.6 g. (52%) of pure III_{me}, identical with that described under the Friedel–Crafts reaction. On recrystallization of the acid fraction, 1.2 g. (25%) of pure 2-fluoro-6-(1-naphthoyl)benzoic acid (IV), m.p. 144–145°, was obtained. The pure methyl ester of IV, IV_{me}, m.p. 94–95°, was prepared with diazomethane and was recrystallized from methanol.[15]

In an analogous reaction 2-naphthylmagnesium bromide was added to 3-fluorophthalic anhydride to yield a mixture, m.p. 135–157°, of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 2-fluoro-6-(2-naphthoyl)benzoic acid (V) in 71–75% yield (two runs). This mixture was converted into the mixture of methyl esters by treatment with diazomethane and was analyzed by the n.m.r. method described above[13]; II_{me} had a τ value of 6.35 and V_{me}, a τ value of 6.41. The ratio of II_{me} to V_{me} was about 3:2. The average yields of II and IV are thus calculated to be about 43 and 30%, respectively.

Separation of esters II_{me} and V_{me} by the sulfuric acid method[14] was not very successful. However, pure V, m.p. 160–161°, was obtained from the acidic portion by several recrystallizations from toluene. The methyl ester V_{me}, m.p. 103–104°, was obtained by treatment with diazomethane.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7; F, 6.5. Found for IV: C, 73.5; H, 3.8; F, 6.3. Found for V: C, 73.8; H, 3.9; F, 6.8.

Anal. Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.2; F, 6.2. Found for IV_{me}: C, 74.2; H, 4.4; F, 6.0. Found for V_{me}: C, 74.3; H, 4.2; F, 6.5.

Proof of Structure of Keto Acids.—The structure of each acid, II–V, was established by decarboxylation to a fluorophenyl naphthyl ketone by boiling with copper powder in quinoline (yields 76–82%), followed by comparison with an authentic sample prepared by reaction of a Grignard reagent with a nitrile. The ketones were converted into the 2,4-dinitrophenylhydrazones (DNPH); identity of the ketones was established by mixture melting point determinations of the ketones and the DNPH derivatives and by comparison of the infrared spectra of the ketones and the DNPH derivatives. The work is summarized in Table I.

In previous work[5] o-fluorophenyl 1-naphthyl ketone was reported as an oil, b.p. 212–213° at 6 mm., which gave a DNPH derivative, m.p. 282–283°, and m-fluorophenyl 1-naphthyl ketone was reported as a solid, m.p. 122–123°, which formed a DNPH derivative, m.p. 262–264°. Actually o-fluorophenyl 1-naphthyl ketone is a solid, m.p. 58.5–60.0°, which forms a DNPH derivative, m.p. 283–285°, and m-fluorophenyl 1-naphthyl ketone melts at 60–61° and forms two DNPH derivatives, m.p. 220–222° and 258–260°. Since the m-fluorophenyl 1-naphthyl ketone reported before[5] was formed by a Friedel–Crafts condensation of m-fluorobenzoyl chloride with naphthalene in o-dichlorobenzene, it must have been[16] m-fluorophenyl 2-naphthyl ketone, since we have shown that 3-fluorophthalic anhydride condenses mainly at the 2-position of naphthalene. The melting point of 122–123° reported[5] for m-fluorophenyl 1-naphthyl ketone is in agreement with the melting point of 122–123° found in this paper for m-fluorophenyl 2-naphthyl ketone.

All ketones in Table I were recrystallized from methanol.

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(14) Compare M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1537 (1941).

(15) In the Bergmann and Bentov reference cited previously in ref. 7, this methyl ester is stated to melt at 115°. Our ester, IV_{me}, m.p. 94°, is a polymorphic form as we obtained the same melting point when we prepared this ester from a pure sample of IV supplied by Professor Bergmann. Both the acid IV and the methyl ester IV_{me} had infrared spectra identical with those prepared from the acid sent to us.

(16) The sample labeled m-fluorophenyl 1-naphthyl ketone, m.p. 122–123°, in our sample box when re-examined proved to be identical with our sample of m-fluorophenyl 2-naphthyl ketone, m.p. 122–123°, prepared from 2-naphthonitrile.