[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY OF THE HEBREW UNIVERSITY, HADASSAH MEDICAL SCHOOL, AND THE SCIENTIFIC DEPARTMENT OF THE ISRAELI MINISTRY OF DEFENSE]

Synthesis and Properties of ω-Fluoroacetophenone

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ω-Fluoroacetophenone (I) can be obtained in good yields by the Friedel–Crafts method, if the reaction with fluoroacetyl chloride is carried out rapidly in a homogeneous medium, *e.g.*, methylene chloride. Compound I can be converted into 1,1-diphenyl-2-fluoroethanol, if the Grignard reaction with phenylmagnesium bromide is carried out rapidly and at low temperature. Under more drastic conditions intramolecular rearrangement converts the carbinol into desoxybenzoin. Only under special precautions can compound I be reduced to 1-phenyl-2-fluoroethanol by lithium aluminum hydride. The same product is also obtained by catalytic reduction. Toxicological data for some of these compounds are reported.

Since acetophenone is metabolized in dogs and rabbits mainly to hippuric acid and derivatives of phenylmethylcarbinol,[1,2] it appears that benzoic acid is one of the breakdown products in the mammalian organism. A similar behavior has been demonstrated for 3-acetylpyridine.[3,4]

Although the exact mechanism of this conversion is unknown, a possible route consists in the carboxylation of acetophenone to benzoylacetic acid and degradation of the latter to benzoic and acetic acids, in analogy to the metabolic interconversion of the system pyruvate–oxaloacetate. It was considered possible that ω-fluoroacetophenone may undergo, at least in part, an analogous transformation and thus serve as *in vivo* source of fluoroacetate. It was therefore decided to study the metabolism of this ketone in detail. In the present paper we describe the synthesis and certain reactions of ω-fluoroacetophenone and report also a few toxicological data.

ω-Fluoroacetophenone (I) is usually prepared by the Friedel–Crafts reaction of fluoroacetyl chloride.[5,6] Although yields of 45% have been reported, we could not obtain more than 20% of purified I, the main difficulty consisting in the simultaneous formation of considerable quantities of ω-chloroacetophenone. Separation of the two products by repeated fractionation is very cumbersome and unpleasant and leads to considerable losses of material. A number of other methods, *e.g.*, the reaction between diphenylcadmium and fluoroacetyl chloride,[7] the condensation of the latter with phenyllithium or dry distillation of an intimate mixture of calcium benzoate and fluoroacetate, either failed to produce the desired ketone or else gave unsatisfactory yields due to contamination with the chloro derivative.

In view of these failures the Friedel–Crafts reaction was investigated more thoroughly. It appeared possible that the halogen exchange was due to prolonged contact of I with solid catalyst. Therefore we tried a solvent, in which aluminum chloride is sufficiently soluble, and added only the amount of benzene required for the reaction itself. It was found that the condensation in ethylene dichloride gave 60–70% of I and in methylene chloride 75–85%. Only traces of chloroacetophenone were formed under the conditions described in the Experimental Part and a single vacuum distillation permitted the isolation of pure, crystalline ω-fluoroacetophenone of m.p. 27–28°. With nitrobenzene as solvent the desired product could not be obtained.

Since ketone I has now become easily available, we studied its chemical behavior and report here on some typical reactions of its carbonyl group. Characterization of I has been achieved previously by its crystalline addition compound with pyridine.[8] However, pure I gives the usual carbonyl derivatives. The β-fluorine is not attacked even by refluxing 5 hours with semicarbazide. The 2,4-dinitrophenylhydrazone, m.p. 215–216°, and the semicarbazone, m.p. 189–190°, make ω-fluoroacetophenone easily distinguishable from acetophenone and its chloro or bromo derivative. As is to be expected, the aliphatic fluorine has no influence on the ultraviolet absorption spectrum, which is practically identical with that of acetophenone. The infrared spectra of I and related compounds will be reported in another paper.

The result of interaction of I with phenylmagnesium bromide depends on the reaction conditions used: If the ether solution is refluxed and left overnight before decomposition, desoxybenzoin is the only product. If, however, the ketone is added to the Grignard solution at 0° and the mixture decomposed immediately, a 65% yield of 1,1-diphenyl-2-fluoroethanol (II) is obtained. It is thus reasonable to assume that the magnesium alkoxide of II is the primary product, but that under sufficiently drastic conditions magnesium bromide–fluoride is split off and simultaneously—by a concerted mechanism—a phenyl group is shifted to give desoxybenzoin (reaction scheme A). Similar results were obtained in experiments with ω-chloroacetophenone. It is noteworthy that rearrangement of 1,1-diphenylethylene oxide has been reported to yield diphenylacetaldehyde.[9] The carbinol II resists dehydration obstinately. It is recovered unchanged after refluxing with 25% sulfuric acid, or with a solution of iodine in xylene; or, after heating, with or without phthalic anhydride, to 220°. Upon treatment with concd. sulfuric acid at room temperature a crystalline

(1) H. Thierfelder and K. Z. Daiber, *Z. physiol. Chem.*, **130**, 380 (1923).

(2) G. Quick, *J. Biol. Chem.*, **80**, 521 (1928).

(3) W. T. Beher, W. M. Holliday and Oliver H. Gaebler, *ibid.*, **198**, 573 (1952).

(4) W. T. Beher and W. L. Anthony, *ibid.*, **203**, 895 (1953).

(5) E. Gryszkiewicz-Trochimowski, A. Sporziński and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

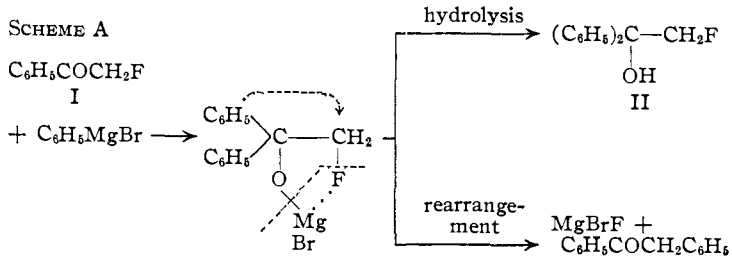
(6) W. E. Truce and B. H. Sack, THIS JOURNAL, **70**, 3959 (1948).

(7) One of the referees reports that he obtained by this method a 30% yield of phenacyl fluoride and 50% of desoxybenzoin.

(8) P. Ch. Ray, H. Ch. Goswami and A. Ch. Ray, *J. Indian Chem. Soc.*, **12**, 93 (1935).

(9) A. Klages and J. Kessler, *Ber.*, **39**, 1753 (1906).

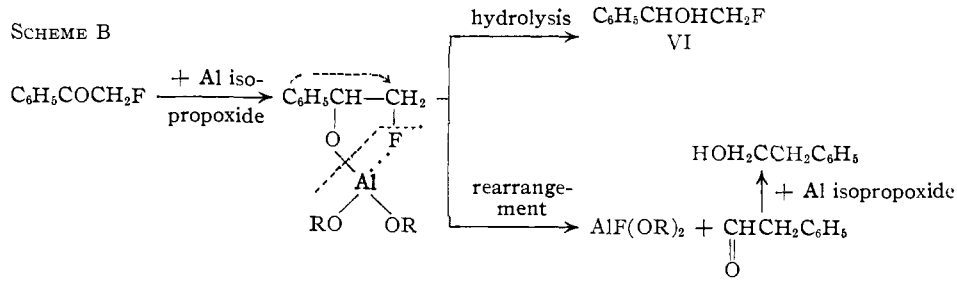
SCHEME A



dimer of 1,1-diphenylvinyl fluoride, of m.p. 152–153°, is obtained in 33% yield. 1,1-Diphenylethylene can be converted either into an open-chain dimer III or an indane derivative (IV).[10] Comparison of the absorption spectra of III and IV with our fluorinated dimer (Fig. 1) supports structure V for the latter. Again the fluorine atoms have very little influence on the position of the absorption bands.

Reduction of ω-fluoroacetophenone with aluminum isopropoxide has been reported to yield mainly β-phenylethanol.[6] This result has been explained by the assumption that styrene oxide is an intermediate. In the light of our observations with 1,1-diphenyl-2-fluoroethanol it appears likely that here again the aluminum alkoxide of the expected 1-phenyl-2-fluoroethanol is the primary product, from which aluminum fluoride–alkoxide is split off easily upon warming. The intermediate simultaneously shifts its phenyl group to the β-carbon, as illustrated in scheme B. It was therefore concluded that only under very mild conditions would it be possible to isolate the still unknown 1-phenyl-2-fluoroethanol (VI). Therefore ω-fluoroacetophenone was reduced with lithium aluminum hydride at 0° and the mixture decomposed immediately, after the addition of the ketone was finished. In this way an 80% yield of VI could be secured. The new alcohol was characterized as its *p*-nitrobenzoate. When the reaction was carried out at 35°, only a mixture of halogen-free products was obtained. The catalytic reduction of acetophenone usually stops at the carbinol stage, although small amounts of ethylbenzene are also obtained.[11] Reduction of I with palladium-on-charcoal proceeds more rapidly in isopropyl alcohol than in ethanol and gives high yields of VI, if the starting material is carefully purified and acid free. Otherwise the uptake of hydrogen does not stop after one mole and considerable amounts of dehalogenated products may be formed. This result can be duplicated by addition of hydrochloric acid to the reduction mixture, which now absorbs two or even more moles of hydrogen. It is, however, remarkable, that 1-phenyl-2-fluoroethanol, once it has been isolated, is not attacked at all under the same conditions. Experiments on the conversion of this alcohol to β-fluorostyrene will be reported in a subsequent paper.

SCHEME B



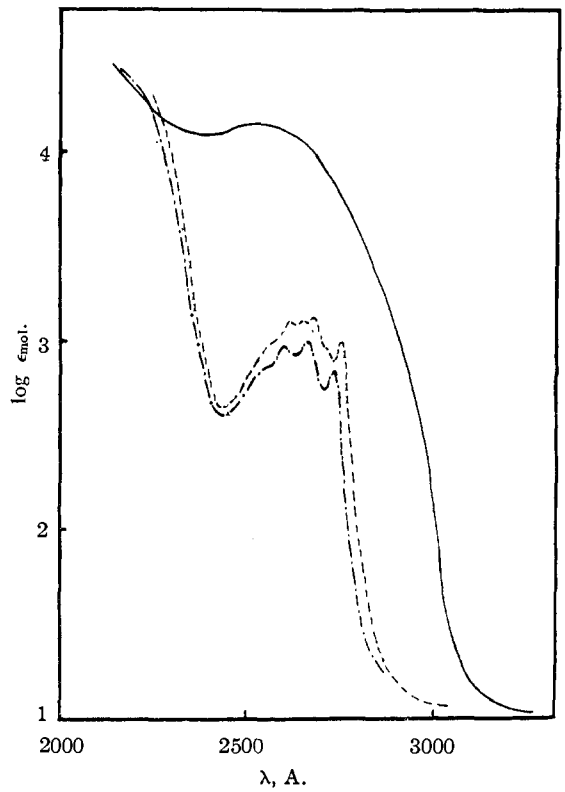


Fig. 1.—Ultraviolet absorption spectra in 95% alcohol: ———, open-chain dimer of 1,1-diphenylethylene (III), m.p. 112°; - - - - -, cyclic dimer of 1,1-diphenylethylene (IV), m.p. 140°; - . - . -, dimer of 1,1-diphenylvinyl fluoride (V), m.p. 152–153°.

Although we did not succeed with the preparation of 1,1-diphenylvinyl fluoride,[12] its ability to undergo condensation with maleic anhydride could be tested with the carbinol II, since it has been shown previously that 1,1-diphenylethanol behaves in this reaction like 1,1-diphenylethylene.[13] When II was heated with maleic anhydride to 200°, it produced directly the known 4-phenylnaphthalene-1,2-dicarboxylic acid anhydride (VII). The same product was isolated from the reaction of 1,1-diphenyl-2-chloroethanol. The condensation of

(10) E. Bergmann and H. Weiss, *Ann.*, **480**, 49 (1930).

(11) F. Straus and H. Grindel, *ibid.*, **439**, 278 (1924).

(12) O. Dimroth and W. Bockmueller, *Ber.*, **64**, 516 (1931), prepared this compound from diphenylethylene and lead tetrafluoride.

(13) F. Bergmann, J. Szmuszkowicz and G. Fawaz, THIS JOURNAL, **69**, 1773 (1947).

the fluoro derivative thus supplements the experiments with 1,1-diphenylvinyl chloride[14] and bromide,[15] reported earlier. The direct conversion of all three halogenides into the aromatic anhydride VII makes it doubtful whether the reaction in these cases follows the same course as the classical Wagner-Jauregg reaction, in which 1,1-diphenylethylene first forms a bis-adduct with maleic anhydride.[16]

Toxicological Data.—The minimum lethal doses for white mice and rats of acetophenone, ω-fluoroacetophenone and 1-phenyl-2-fluoroethanol (VI) are reported in Table I. Compound I is 3–4 times more toxic than acetophenone. It also differs from the latter by the absence of any hypnotic effect. On the contrary, I produces hyperexcitability in mice and convulsive states in rats, which are very similar to fluoroacetate poisoning. VI in lethal doses may produce superficial sleep, but the reflexes are preserved. The much higher toxicity of I, as compared to VI, which is a possible metabolite of I, indicates either that ω-fluoroacetophenone is toxic as such or else that it is metabolized—at least in part—by some other route than reduction of its carbonyl group. Experiments on the isolation of metabolites of I and VI will be reported in a future publication.

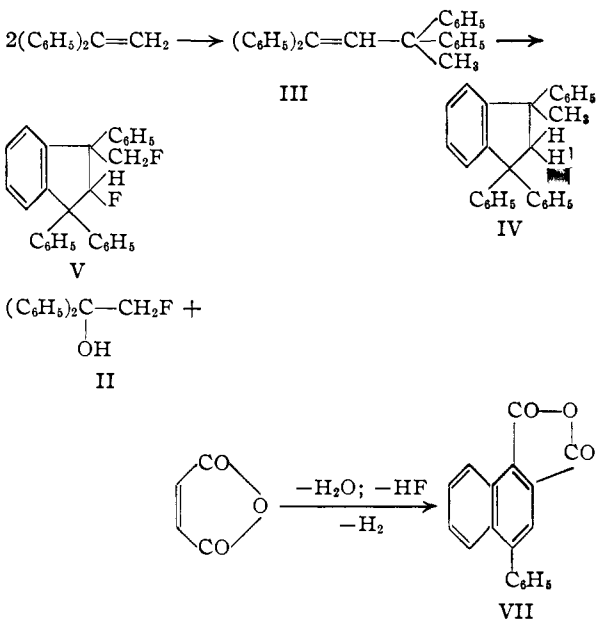


TABLE I

MINIMUM LETHAL DOSE (MG./KG.) OF VARIOUS COMPOUNDS FOR RATS AND MICE

Compound	Mice	Rats
Acetophenone	900	750
ω-Fluoroacetophenone	225	225
1-Phenyl-2-fluoroethanol	~700[a]	~450[a]

[a] Whereas acetophenone and ω-fluoroacetophenone show a clear relationship between dose and mortality, the results with compound VI were erratic.

(14) F. Bergmann and J. Szmuszkowicz, THIS JOURNAL, 72, 1035 (1950).

(15) F. Bergmann and J. Szmuszkowicz, *ibid.*, 69, 1777 (1947).

(16) Th. Wagner-Jauregg, *Ber.*, 63, 3218 (1930); *Ann.*, 494, 1 (1932).

Experimental Part

All m.p.'s are uncorrected.

1. **Synthesis of ω-Fluoroacetophenone (I).**—Finely powdered aluminum chloride (250 g.) was stirred with methylene chloride (1 l.) for 30 min. Fluoroacetyl chloride[17] (80 g.) in methylene chloride (300 cc.) was added at once and stirring continued for another 30 min. The dark brown solution was decanted from the solid residue into a three-necked flask and cooled to 0°. During 15 min. a mixture of benzene (80 cc.) and methylene chloride (160 cc.) was added dropwise under vigorous stirring, which was continued for another 20 min. The mixture was poured *immediately* onto ice and hydrochloric acid, the organic layer separated, washed with water and bicarbonate and dried over calcium chloride. After removal of the solvent the reaction product was fractionated *in vacuo* by means of a short Vigreux column. ω-Fluoroacetophenone (I) distils at 65–70° (1 mm.) and crystallizes spontaneously in big plates of m.p. 27–28°, yield 93 g. (81%).

Anal. Calcd. for C_8H_7OF: C, 69.6; H, 5.1. Found: C, 69.9; H, 5.2.

The semicarbazone crystallizes from butyl acetate as long needles, m.p. 190°. When I is refluxed with semicarbazide acetate in ethanol for 5 hours, the same product is obtained.

Anal. Calcd. for $C_9H_{10}ON_3F$: C, 55.4; H, 5.1. Found: C, 55.2; H, 5.4.

The 2,4-dinitrophenylhydrazone crystallizes from xylene in orange-red, long lancets of m.p. 213–214°.

Anal. Calcd. for $C_{14}H_{11}O_4N_4F$: C, 52.8; H, 3.5. Found: C, 52.7; H, 3.3.

2. **Synthesis and Reactions of 1,1-Diphenyl-2-fluoroethanol (II).**—To a Grignard solution, prepared from bromobenzene (20 g.), magnesium (2.5 g.) and ether (50 cc.), was added dropwise at 0° a solution of ω-fluoroacetophenone (14 g.) in ether (25 cc.) during 15 min. Immediately thereafter a solution of ammonium chloride in ice-water was added slowly. After separation of the solvent the aqueous layer was extracted three times with ether. The combined ethereal extracts were dried over sodium sulfate and the solvent distilled off. Fractionation *in vacuo* gave a colorless oil of b.p. 70–75° (0.2 mm.), which solidified rapidly. 1,1-Diphenyl-2-fluoroethanol (II) crystallized from ligroin in colorless prisms of m.p. 71–72°, yield 14 g. (65%).

Anal. Calcd. for $C_{14}H_{13}OF$: C, 77.8; H, 6.0. Found: C, 77.8; H, 6.2.

If the ketone I was added to the warm Grignard solution, the mixture refluxed for 30 min. and then left overnight, only desoxybenzoin, m.p. 56°, could be isolated. It was identified as its semicarbazone of m.p. 148°.

The carbinol II was recovered unchanged after refluxing with 25% sulfuric acid or with a solution of iodine in xylene, but was also decomposed partly to yield low-boiling liquids. II dissolves in concd. sulfuric acid with red-brown color. This solution (1 g. in 20 cc. of acid) was left at room temperature for 24 hours, then decomposed with ice and extracted with benzene. The organic layer was washed with water and bicarbonate and dried over sodium sulfate. After evaporation of the solvent a solid residue remained, which crystallized from butanol in long rods of m.p. 152–153° (V), yield 0.3 g. (33%).

Anal. Calcd. for $(C_{14}H_{11}F)_2$: C, 84.8; H, 5.6; mol. wt., 396. Found: C, 84.5; H, 5.8; mol. wt. (cryoscopic method in benzene), 384, 406.

The carbinol II (1 g.) and maleic anhydride (8 g.) were heated to 195–200° for 6 hours. The dark-brown mass was dissolved in 5 cc. of hot acetic acid and this solution left for 48 hours, whereupon it deposited intense yellow crystals. After crystallization from xylene 0.3 g. of yellow cubes was obtained. The substance showed a m.p. of 168°, which was not depressed by admixture of an authentic specimen of 4-phenylnaphthalene-1,2-dicarboxylic acid anhydride (VII).[18]

3. **Reduction of ω-Fluoroacetophenone. (a) With Lithium Aluminum Anhydride.**—This reagent (1.8 g.) in absolute ether (90 cc.) was stirred and cooled to 0°. A solution of ω-fluoroacetophenone (15 g.) in ether (50 cc.) was added very slowly over 90 min. and the mixture decomposed 10 min. later with a solution of sulfuric acid (2 g.) in 30 cc.

(17) W. E. Truce, THIS JOURNAL, 70, 2828 (1948).

of ice-water. After separation of the organic layer, the aqueous medium was extracted three times with ether. The combined ethereal extracts were washed and dried as usual. Fractional distillation yielded 1-phenyl-2-fluoroethanol (VI) as a colorless oil of b.p. 55–59° (2 mm.), yield 12 g. (79%). It is remarkable that the b.p. of VI is about 30° below that of phenylmethylcarbinol.

Anal. Calcd. for C_8H_9OF: C, 68.6; H, 6.4; F, 13.6. Found: C, 68.6; H, 6.6; F, 13.8.

The carbinol VI gave a crystalline *p*-nitrobenzoate after treatment with *p*-nitrobenzoyl chloride in pyridine. The ester crystallized from ethanol in rods of m.p. 92–93°.

Anal. Calcd. for $C_{15}H_{12}O_4NF$: C, 62.3; H, 4.2. Found: C, 62.3; H, 4.3.

(b) **With Hydrogen and Palladium.**—ω-Fluoroacetophenone (9 g.) in isopropyl alcohol (35 cc.) was reduced at 18° and 693 mm. in the presence of 1.5 g. of palladium-on-charcoal (5%). During 4 hours 1830 cc. was absorbed (calcd. 1760 cc.). The catalyst was filtered off and the weakly acidic solution neutralized with sodium carbonate. Fractionation gave 6.5 g. (71%) of a colorless oil of b.p. 70–75° (12 mm.). Its *p*-nitrobenzoate proved identical with the ester of VI, described under (a).

When HCl was added to the reduction medium, hydrogen absorption continued beyond the theoretical amount and the yield of VI was correspondingly decreased. When the carbinol VI (4 g.) in isopropyl alcohol (25 cc.) was treated under the same conditions as fluoroacetophenone, no hydrogen was absorbed during 4 hours and the starting material was recovered quantitatively.

4. **1,1-Diphenyl-2-chloroethanol.**—This carbinol was prepared from ω-chloroacetophenone (6.5 g.) and phenylmagnesium bromide under the conditions described for the corresponding fluoro derivative. Fractionation gave a colorless oil of b.p. 70–75° (0.3 mm.), which solidified immediately. 1,1-Diphenyl-2-chloroethanol crystallized from petroleum ether–ligroin in prisms of m.p. 65.5°, yield 7.5 g. (76%). The carbinol (1 g.) and maleic anhydride (8 g.) were heated to 195–200° for 6 hours and the light-brown magma dissolved in a small volume of acetic acid. After 48 hours, 0.5 g. of yellow crystals was collected, of m.p. 168–169°, not depressed by admixture of authentic 4-phenylnaphthalene-1,2-dicarboxylic acid anhydride.

The absorption spectra were measured in 95% ethanol with a Beckman ultraviolet spectrophotometer. Carbon and hydrogen determinations for organic fluorine derivatives were carried out by the method of Bodenheimer and Goldstein.[18]

We wish to thank Mrs. M. Goldstein for the micro-analyses and Miss H. Weiler for the spectrographic data.

(18) W. Bodenheimer and M. Goldstein, *Bull. Res. Council Israel*, III, 53 (1953).

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXVIII.[1] 9,10-Dialkylphenanthrenes by Cyclization of Ketones

BY CHARLES K. BRADSHER AND WINSTON J. JACKSON, JR.[2]

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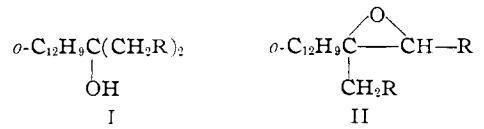
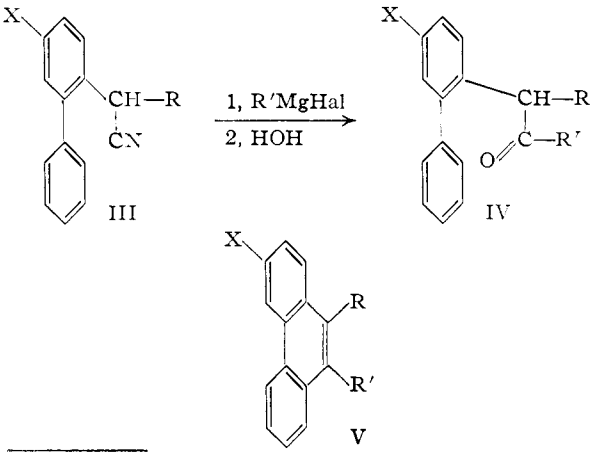
The cyclization of 2-biphenylyl ketones (IV) can be extended to cases where R and R′ are normal alkyl groups. Where R or R′ is isopropyl, cyclization is accompanied by loss of the isopropyl group. A similar loss of isopropyl group has been observed in an olefin oxide type cyclization.

The first 9,10-dialkylphenanthrenes were prepared by Zincke and Tropp[3] who treated phenanthraquinone with alkyl Grignard reagents and dehydrated the resulting glycol to a 10,10-dialkyl-9-phenanthrone. Where the R group was methyl or ethyl, reduction and rearrangement with hydriodic acid yielded the corresponding dialkylphenanthrene, but this reaction failed where R was the propyl group. The same two hydrocarbons were obtained by Meerwein[4] by reduction and rearrangement of 9-methyl-9-acetylfluorene and 9-ethyl-10-propionylfluorene.

Another method[5] involves use of carbinols I which are obtained by the addition of biphenylylmagnesium iodide to symmetrical ketones. Dehydration and epoxidation of the carbinols yields the epoxides II which may be cyclized to 9,10-dialkylhydrocarbons (V, X = H; R′ = CH_2R). This is clearly a method which cannot be adopted to the unambiguous synthesis of any desired 9,10-dialkylphenanthrene derivative.

The method which has been developed recently[6,7] for the synthesis of 9-alkyl-10-arylphenanthrene derivatives gave promise of being sufficiently general to permit the preparation of diverse kinds of 9,10-dialkylphenanthrenes. The present investigation was undertaken to determine the limitations of the method.





(1) For the preceding communication of this series, see THIS JOURNAL, **76**, 734 (1954).

(2) Public Health Service Fellow of the National Cancer Institute, 1950–1952.

(3) T. Zincke and W. Tropp, *Ann.*, **362**, 242 (1908); H. Meerwein, *ibid.*, **396**, 200 (1913).

(4) H. Meerwein, *ibid.*, **405**, 129 (1914).

(5) C. K. Bradsher and S. T. Amore, THIS JOURNAL, **66**, 2016 (1943); **66**, 1980 (1944).

(6) C. K. Bradsher and W. J. Jackson, Jr., *ibid.*, **73**, 3235 (1951).

(7) C. K. Bradsher and W. J. Jackson, Jr., *ibid.*, **74**, 4880 (1952).