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Reactions of Active Methylene Compounds in Pyridine Solution. III. An Essential Variance with Reactions in Alcohol Solution[1]

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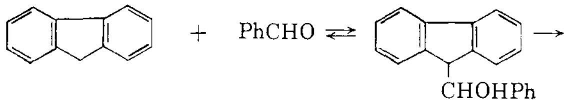
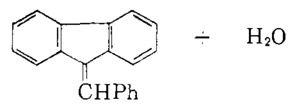
The base-catalyzed hydrogen-tritium exchange of indene and fluorene has been found to be much faster in pyridine than in alcohol. Comparison of the rate of exchange of fluorene with that of its reaction with benzaldehyde, both in alcohol containing sodium ethoxide, lends support to the view that carbanions are not present in this medium to any appreciable extent, in contrast with the conditions prevailing in pyridine (in the presence of Triton B). A concerted mechanism is proposed for the condensation, as distinct from the two-step carbanion mechanism suggested for reaction in pyridine. As a complement to the isotope-exchange experiments, the racemization of an optically active fluorene derivative has been studied and found to be much faster in pyridine than in alcohol. The rapid racemization in pyridine serves to demonstrate the configurational instability of the carbanion.

It has been reported in Part I of this series[2] that hydrocarbons of the cyclopentadiene series show pronounced reactivity in pyridine solution in the presence of hydroxide ions, supplied in the form of benzyltrimethylammonium hydroxide (Triton B). Of special interest is the easy autoxidation of these hydrocarbons at ordinary or low temperatures to give ketones, tertiary carbinols and tertiary hydroperoxides, according to the nature of the starting materials and to the conditions used. No reaction took place when the autoxidation of either indene or fluorene was attempted in alcoholic solution containing hydroxide or ethoxide ions. While such solutions are colorless, alkaline pyridine solutions of all hydrocarbons belonging to the above group are invariably colored. It may further be noted that hydrocarbons, including diphenyl- and triphenylmethane, which showed no reaction in pyridine in the presence of Triton B, also failed to develop a color under these conditions.

Another manifestation of high reactivity is to be found in the condensation of indene and fluorene with aldehydes and ketones.[1] While the base-catalyzed (aldol-type) reaction of these hydrocarbons with aldehydes, particularly aromatic, to give benzofulvenes and dibenzofulvenes (*e.g.*, II) can be, and commonly is, performed in alcoholic solution, the reaction ordinarily requires heating in order to proceed at an appreciable rate. This requirement accounts at least partially for the failure to isolate the carbinols (*e.g.*, I) generally assumed to be intermediates in the reaction, as these carbinols are readily dehydrated under the alkaline conditions used. In pyridine, the reaction is rapid at or below room temperature, and carbinols can be isolated in substantial yields.



I



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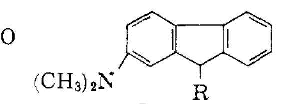
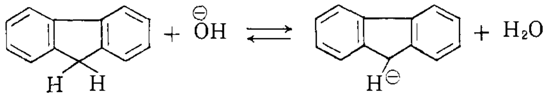
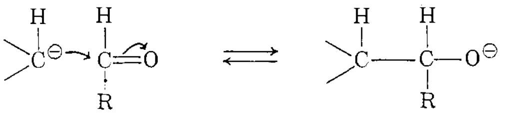


III

The above observations, in particular those relating to color phenomena and to autoxidation, strongly suggest that in pyridine solution hydrocarbons of the cyclopentadiene series produce (colored) carbanions in appreciable concentration (eq. 1) and that under these conditions reactions of the Michael and aldol types, commonly classified as carbanion reactions,[3] actually proceed through carbanions, as depicted by the familiar representation of the condensation with aldehydes (eq. 2).

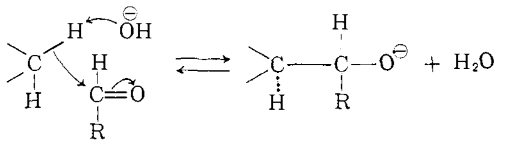


(1)



(2)

On the other hand, the behavior of the above hydrocarbons in alcoholic solution under comparable conditions, in particular the absence of autoxidation, calls in question the existence of any appreciable amount of carbanions in this system. In order to account for reactions taking place in this medium, a one-step course is suggested, to replace the two-step course (eq. 1 and 2) postulated for reactions in pyridine. Illustrated for the reaction with aldehydes, it consists of a simultaneous attack at the C-H bond of the active methylene group by the basic catalyst and the aldehyde (eq. 3). This assumption is tantamount to supposing that heterolytic fission of the C-H bond concerned is considerably more difficult in alcohol than in pyridine, so that in the former solvent the removal of a proton by the base requires the assistance of the polar carbonyl group. It is not meant to imply, however, that the concerted mechanism may not operate in pyridine parallel to the two-step mechanism, as it seems reasonable to assume that the same (solvent) factor that promotes the production of ions should also facilitate reaction according to eq. 3. The relative importance of the concerted mech-



(3)

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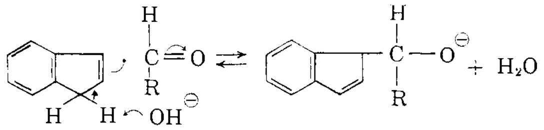
[1] Part II, E. Ghera and Y. Sprinzak, THIS JOURNAL, 82, 4945 (160).

[2] Y. Sprinzak, *ibid.*, 80, 5449 (1958).

[3] J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 200.

anism can be expected to be greater in indene than in fluorene, as the allylic system in the former probably allows for a simultaneous attack at the α- and γ-carbon atoms (eq. 4).


(4)

In view of the ease with which acids are known to exchange their acidic hydrogen,[4] the occurrence of the ionization process 1 would imply that the hydrocarbons under discussion should exchange hydrogen rapidly when dissolved in pyridine in the presence of hydroxide ions. Furthermore, since unsuccessful attempts to prepare optically active metal-organic compounds (metalated at the asymmetric carbon) have made it highly probable that carbanions are configurationally unstable,[5,6] it was to be expected that a 9-substituted optically active fluorene derivative should racemize rapidly in the above medium. We therefore have carried out (a) hydrogen-tritium exchange experiments with fluorene and indene,[7] performed at room temperature in pyridine and in alcohol under comparable conditions and supplemented by condensation experiments of fluorene with benzaldehyde in alcohol; and (b) racemization experiments of optically active 9-benzyl-2-dimethylaminofluorene (III, R = $PhCH_2$) in pyridine and in benzyl alcohol.[8] The racemic amine, chosen for its easy preparation[9] from 2-dimethylaminofluorene, was readily resolved through its *d*-10-camphorsulfonate, a procedure previously employed for the resolution of the 9-methyl derivative (III, R = Me).[3] Advantageously the optically active compound had a high specific rotation.

The results of exchange experiments (Table I) show a striking difference between the rates of exchange in the two solvents. Thus, whereas 80% exchange was observed with fluorene in pyridine and Triton B after 15 minutes, only 7% exchange could be detected in alcohol and sodium ethoxide after 24 hours.[10]

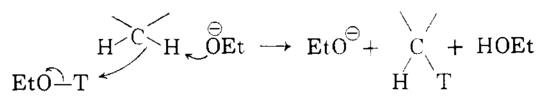
TABLE I

HYDROGEN-TRITIUM EXCHANGE[a]

Substance	Solvent	Catalyst	Time, hr.	Exchange,[b] %
Fluorene[c]	Tritioalcohol	EtONa	24	7
Fluorene	Tritioalcohol	EtONa	336	68
Fluorene	Pyridine–T_2O	Triton B	0.25	79
Fluorene	Pyridine–T_2O	Triton B	4	100
Indene[d]	Tritioalcohol	EtONa	40	56
Indene	Pyridine–T_2O	Triton B	0.25	108
Indene	Pyridine–T_2O	Triton B	4	107
9-Benzyl-2-dimethylaminofluorene[e]	Pyridine–T_2O	Triton B	4	67

[a] Performed at room temperature (23°). [b] The average accuracy of the measurement was approximately ±10% of the given values. [c] Two exchangeable hydrogens. [d] Three exchangeable hydrogens. [e] One exchangeable hydrogen.

The question naturally arises whether the slow exchange observed in alcohol does not indicate merely that process 1, although slow in this medium, is nevertheless operative here just as in pyridine. We are inclined to believe, however, (see below), that exchange in alcohol proceeds mainly, if not wholly, by a concerted mechanism (eq. 5), analogous to that proposed for the condensation with aldehydes (eq. 3) and identical with a mechanism considered by de Salas and Wilson in connection with their study of the isomerization of methyleneazomethines.[11]


(5)

In an attempt to clarify this point, we have carried out the condensation of fluorene with benzaldehyde in alcoholic sodium ethoxide at room temperature, using the same concentrations of fluorene and ethoxide as those employed in the isotope exchange experiments. After a period of 24 hours, no less than 23% of 9-[α-hydroxybenzyl)-fluorene was formed in the reaction.[12] Compared with the figure of 7% obtained in the corresponding exchange experiment, this result seems to support the concerted mechanism theory (eq. 3; $EtO^\ominus$ and EtOH in place of $HO^\ominus$ and H_2O, respectively), as it appears reasonable to assume that had the reaction proceeded through the formation of carbanions (eq. 1; replacement as above) the latter would pick up a proton from the solvent much faster than they would react with the aldehyde (eq. 2).

Equally striking was the effect of the solvent on the rate of racemization of 9-benzyl-2-dimethylaminofluorene (Table II). While in pyridine and Triton B, racemization at room temperature was complete within 15 minutes, it was barely perceptible in benzyl alcohol and sodium ethoxide after 24 hours.

The rapid racemization of 9-benzyl-2-dimethylaminofluorene, beside being complementary to the isotope exchange observed under comparable conditions (Table I), also serves to demonstrate the instability of the pyramidal configuration of

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(4) See, *e.g.*, F. K. Münzberg, *Z. physik. Chem.*, **B31**, 18 (1935).

(5) K. Ziegler and A. Wenz, *Chem. Ber.*, **83**, 354 (1950).

(6) G. Wittig, F. Vidal and E. Bohnert, *ibid.*, **83**, 359 (1950).

(7) Exchange experiments in fluorene and indene have been reported by Kharasch [M. S. Kharasch, W. G. Brown and J. McNab, *J. Org. Chem.*, **2**, 36 (1937); W. G. Brown, M. S. Kharasch and W. R. Sprowls, *ibid.*, **4**, 442 (1939)] and by Shatenshtein [A. I. Shatenshtein, *Doklady Akad. Nauk S.S.S.R.*, **70**, 1029 (1950); A. I. Shatenshtein, N. M. Dykho, E. A. Izrailevich, L. N. Vasil'eva and M. Faivush, *ibid.*, **79**, 479 (1951)]. The former authors have found that fluorene exchanges two hydrogen atoms when kept in alcohol solution at 110° during 69 hours in the presence of sodium hydroxide. The latter authors have carried out exchange experiments with indene and fluorene in deuterioammonia under a variety of conditions; in the presence of potassium amide, fluorene was capable of exchanging practically all of its hydrogens.

(8) This alcohol was used because of the insolubility of the amine in ethanol.

(9) Y. Sprinzak, THIS JOURNAL, **78**, 466 (1956).

(10) Sodium hydroxide or Triton B gave essentially the same results.

(11) E. de Salas and C. L. Wilson, *J. Chem. Soc.*, 1778 (1935).

(12) Apparently dehydration of the carbinol to benzalfluorene was unimportant. This result, undoubtedly due to the use of a very low concentration of catalyst, represents the first isolation of a carbinol in the condensation of fluorene with aldehydes (*cf.* ref. 1).

TABLE II

RACEMIZATION OF 9-BENZYL-2-DIMETHYLAMINOFLUORENE

Solvent	Temp., °C.	Time, hr.	Racem., %
Benzyl alcohol	23	24	4
Benzyl alcohol	23	72	7
Benzyl alcohol	23	336	39
Pyridine	23	0.25	100
Pyridine	−30	1	36
Pyridine	−42	8	88

the carbanion.[13] The slow racemization observed in benzyl alcohol may be explained in terms of the concerted mechanism (eq. 5), assuming that the in-coming proton attacks the asymmetric carbon atom at the side opposite to the out-going proton with resulting inversion of configuration.

Experimental[14]

Dry pyridine and a Triton B solution in pyridine were prepared as described previously.[2] Sodium ethoxide was used in 1.7 *N* solution in ethanol. Acidification of reaction mixtures was by means of acetic acid diluted with the appropriate solvent. All melting points are corrected.

9-Benzyl-2-dimethylaminofluorene (III, R = $PhCH_2$) was prepared in 92% yield by alkylation of 2-dimethylaminofluorene[6] with benzyl alcoholic potassium hydroxide[9]; m.p. 142° (from propanol).

Anal. Calcd. for $C_{22}H_{21}N$: N, 4.68. Found: N, 4.67.

The amine was resolved by recrystallizing its *d*-10-camphorsulfonate from ethyl acetate. The crystalline salt obtained after several recrystallizations was decomposed with a sodium carbonate solution to afford the levorotatory base, $[\alpha]^{18}\mathrm{D}$ −65° (*c* 2.0 in chloroform), m.p. 150–152° (from propanol). Its optical purity was checked by reconverting it to the salt, recrystallizing the latter several times and decomposing it as above.

Anal. Calcd. for $C_{22}H_{21}N$: N, 4.68. Found: N, 4.49.

The mother liquor from the first crystallization of the salt was concentrated to one-half its volume and the crystals deposited on cooling were removed by filtration. The concentrated solution obtained after several repetitions of this operation was evaporated to dryness and the residue was decomposed with sodium carbonate to afford the optically impure base, $[\alpha]^{18}\mathrm{D}$ + 53° (*c* 2.0 in chloroform), m.p. 135–139° (from propanol). *Anal.* Found: N, 4.74.

Exchange Experiments.—The purity of the tritiated compounds was checked by determining their melting points (or boiling points) and refractive indexes. In all cases these properties were found to be identical with those of the starting materials. The tritiated water used, supplied by the Isotope Department of this Institute, showed an activity of 2.7 μc./ml.

Preparation of Samples for Analysis.—The compounds were oxidized over a copper–copper oxide mixture and the water collected reduced with zinc powder at 400°. The tritium activity of the resulting hydrogen was measured on a Geiger–Müller counter.

Tritioalcohol was prepared by dissolving sodium (7 g.) in absolute alcohol (200 ml.) and subsequently adding tritiated water (4.5 ml.). The alcohol was then dried by the method of Manske,[15] using ethyl phthalate. The sample so obtained showed an activity of 5.5×10^{-2} μc./ml.

Fluorene. (a) **In Alcohol.**—Fluorene (0.5 g., m.p. 116–117°) was dissolved in tritioalcohol (25 ml.). A sodium ethoxide solution (0.2 ml.) was added and the mixture was left for the specified period of time. After acidification, the hydrocarbon was recovered by pouring the solution into water, washing with water and recrystallizing from alcohol.

(b) **In Pyridine.**—Fluorene (0.5 g.) was dissolved in pyridine (10 ml.) containing tritiated water (0.3 ml.). After flushing the flask with nitrogen, Triton B (0.03 ml.) was added and the colored solution was left for the specified period of time. The hydrocarbon was recovered as in a.

Indene. (a) **In Alcohol.**—The solution was prepared as described for fluorene, using indene (2.5 g., b.p. 78°(25 mm.), $n^{20}\mathrm{D}$ 1.571), tritioalcohol (25 ml.) and sodium ethoxide (0.3 ml.), and excluding air. After acidification it was poured into water, extracted with ether and distilled *in vacuo* in an atmosphere of nitrogen.

(b) **In Pyridine.**—The quantities used were: indene (2.5 g.), pyridine (50 ml.), tritiated water (1.0 ml.), Triton B (0.2 ml.). The ethereal extract, obtained as in (a), was washed with dilute hydrochloric acid and sodium bicarbonate and distilled as in (a).

9-Benzyl-2-dimethylaminofluorene.—The solution was prepared as in procedure b for fluorene, using the amine (0.8 g.), pyridine (16 ml.), tritiated water (0.3 ml.) and Triton B (0.1 ml.). The amine was recovered similarly and recrystallized from propanol.

Racemization Experiments. (a) **In Benzyl Alcohol.**—The optically active amine (III, R = $PhCH_2$; 0.4 g.) was dissolved in the alcohol (16 ml.) and sodium ethoxide (0.2 ml.) was added in an atmosphere of nitrogen. The reaction was quenched by acidification and the product recovered by pouring the solution into water, filtering the precipitate and recrystallizing it from propanol.

(b) **In Pyridine.**—The amine (0.8 g.) was dissolved in pyridine (16 ml.) and Triton B (0.1 ml.) was added in an atmosphere of nitrogen. The reaction was terminated and the product recovered as in (a).

Condensation of Fluorene with Benzaldehyde.—Sodium ethoxide (2 ml.) was added to a solution of fluorene (8.3 g.) and freshly distilled benzaldehyde (18.6 g.) in absolute alcohol (415 ml.) and the mixture was acidified after keeping at room temperature for 24 hours. The residue obtained after evaporation of the solvent was treated with water, extracted with ether and the ethereal solution dried and evaporated. The excess aldehyde and unreacted fluorene (b.p. 140–145°(8 mm.)) were removed by distillation and the residue (4.1 g.) was treated with hot heptane, filtered after cooling (3.42 g., m.p. 116–120°) and recrystallized from heptane (35 ml.) to afford 3.20 g. (23% yield) of **9-[α-hydroxybenzyl]-fluorene**, m.p. and mixed m.p.[16] 120–121.5°.

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(13) Reference 3, p. 195.

(14) The tritium determinations were performed by the Isotope Department of this Institute.

(15) R. H. Manske, THIS JOURNAL, **53**, 1106 (1931).

(16) A. Kliegl, F. Weng and G. Wiest, *Ber.*, **63**, 1262 (1930)