Inspection of the absorption spectra of the cytochrome *c*–deoxycholate mixtures did not reveal any significant shifts. This was not completely unexpected, however, since the binding of the iron to the protein in cytochrome *c* is very stable from *p*H 3.0 to 11.0. The absence of any effect is in contrast to the action of some other surface active agents on the prosthetic group of cytochrome *c* and of other conjugated proteins.[16,17] Our studies did, however, demonstrate the existence of a 315 mμ peak which was evident after reduction with $H_2$ and platinum black, *i.e.*, in the absence of hydrosulfite. This peak had been observed by Theorell[18] and Schales and Behrnts–Jensen[19] who concluded that it indicated the presence of a sulfoxide group in cytochrome *c*. Lavin, *et al.*,[20] did not observe the peak, and Lemberg and Legge[21] consider it as being due to the presence of sodium hydrosulfite used as a reducing agent. Nevertheless, it is present after reduction with hydrogen and platinum black and in the absence of any sodium hydrosulfite.

The concentration of sodium deoxycholate used in these experiments is well above the "critical" concentrations for the formation of micelles; Ekwall[22] reported it to be 0.014 *M* and McBain[23] reported it to be 0.005 *M*. Because the experimental evidence indicates that the binding is electrostatic, the micellar structure is probably not involved in the primary binding found here. The apparent binding of sodium deoxycholate by cytochrome *c* above its isoelectric point may, however, indicate a secondary interaction involving the micelles of sodium deoxycholate.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

# The Wittig Reaction with Fluorenone. Formation of Cyclopropane Derivatives

BY RAPHAEL MECHOULAM AND FRANZ SONDHEIMER

RECEIVED FEBRUARY 24, 1958

The Wittig reaction between fluorenone (I) and excess of triphenylphosphine-*n*-butylidene (IIa) has been found to yield spiro-(2,3-dipropylcyclopropane-1,9′-fluorene) (IXa). With triphenylphosphinemethylene (IIb), fluorenone gives the previously described spiro-(cyclopropane-1,9′-fluorene) (IXb). The reactions presumably proceed *via* the 9-alkylidenefluorenes (V), since treatment of 9-*n*-butylidenefluorene (Va) with triphenylphosphine-*n*-butylidene (IIa) leads to the same spiro compound IXa as obtained from fluorenone.

In connection with another investigation,[1] we were interested in determining how well the Wittig reaction[2] proceeds between ketones and the triphenylphosphine-alkylidene derived from a saturated primary bromide containing several carbon atoms. With this aim, we studied the reaction between the highly crystalline ketone fluorenone (I) and triphenylphosphine-*n*-butylidene (IIa). The results of this and related experiments are described in this paper.

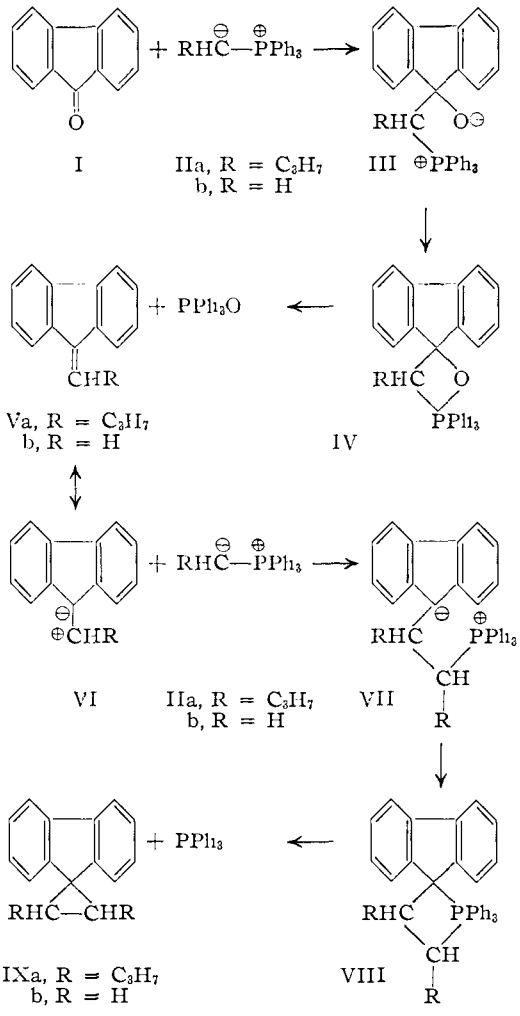
Treatment of *n*-butyl bromide with triphenylphosphine yielded *n*-butyltriphenylphosphonium bromide,[3] m.p. 243°, which was dehydrobrominated with ethereal butyllithium. The resulting solution of triphenylphosphine-*n*-butylidene (IIa) in ether then was allowed to react with fluorenone (I) first at room temperature and then in refluxing tetrahydrofuran, the reagent IIa being in threefold excess. Chromatographic separation produced successively three different substances, the last two of which proved to be, respectively, triphenylphosphine and triphenylphosphine oxide. The first substance, m.p. 45°, obtained in 50% yield, was found to differ from the expected known[4] 9-*n*-butylidenefluorene (Va) of m.p. 55°. It proved to be a hydrocarbon, $C_{21}H_{24}$, *i.e.*, it was derived from the reaction of fluorenone with *two* molar equivalents of triphenylphosphine-*n*-butylidene. The fluorene carbon skeleton has been preserved, since oxidation with chromium trioxide regenerated fluorenone. The ultraviolet spectrum (two highest wave length maxima at 292 and 303 mμ) was very similar to that of a 9,9-dialkylfluorene (*cf.* 9,9-diethylfluorene, which has the corresponding maxima at 292 and 303 mμ).[5] It was significantly different from that of fluorene ($\lambda_{max}$ 288.5 and 300 mμ)[6] and of a 9-monoalkylfluorene (9-methylfluorene, $\lambda_{max}$ 290 and 301 mμ)[6] and quite different from that of a 9-alkylidenefluorene (9-*n*-butylidenefluorene, $\lambda_{max}$ 301 and 311 mμ).[7] That the 9-position was disubstituted was confirmed by the fact that no red color was produced with Triton B in pyridine solution.[8] These facts lead us to propose

(1) *Cf.* F. Sondheimer and R. Mechoulam, THIS JOURNAL, **79**, 5029 (1957); **80**, 3087 (1958).
(2) *Cf.* G. Wittig, *Experientia*, **12**, 41 (1956); *Angew. Chem.*, **68**, 505 (1956), and earlier references cited there.
(3) Badische Anilin und Soda-Fabrik, German Patent 824,047 (*C. A.* **49**, 6998 (1955)).
(4) R. F. Schultz and C. F. Smullin, THIS JOURNAL, **62**, 2904 (1940); Y. Sprinzak, *ibid.*, **74**, 2116 (1952).
(5) E. J. Greenhow and D. McNeil, *J. Chem. Soc.*, 3204 (1956).
(6) E. J. Greenhow, D. McNeil and E. N. White, *ibid.*, 986 (1952).
(7) S. Wawzonek and E. Dufek, THIS JOURNAL, **78**, 3530 (1956).
(8) Fluorene derivatives containing one or two hydrogen atoms at C-9 give a red color under these conditions (Y. Sprinzak, Congress

the spiro-(2,3-di-*n*-propylcyclopropane-1,9′-fluorene) structure IXa for this substance.

Although the compound IXa was unknown, spiro-(cyclopropane-1,9′-fluorene) (IXb) has been described.[5,6,9] We therefore allowed fluorenone (I) to react with excess triphenylphosphinemethylene (IIb). This reaction led to triphenylphosphine, triphenylphosphine oxide and a substance which proved to be identical with an authentic sample of the spiro compound IXb. By analogy, the cyclopropane structure IXa assigned to the product from fluorenone and triphenylphosphinebutylidene must be correct.[10] As expected, the ultraviolet spectra of the two spiro compounds IXa and IXb are almost identical.

The formation of the spiro compounds readily can be explained if it is assumed that the normal reaction[2] between the triphenylphosphine-alkylidene and fluorenone takes place first, leading *via* the intermediate III and/or IV to the 9-alkylidenefluorene V and triphenylphosphine oxide. The semicyclic double bond in dibenzfulvenes of type V is strongly polarized (the polarization, as in VI, being of course in the opposite sense than in the corresponding ketones) and consequently it behaves like a carbonyl function in reactions with Grignard reagents, lithium aluminum hydride, etc.[11] Similarly, the 9-alkylidenefluorene V reacts with the triphenylphosphine-alkylidene II to give an intermediate such as VII and/or VIII, which then decomposes to yield the cyclopropane derivative IX and triphenylphosphine. Support for this mechanism is provided by the fact that 9-*n*-butylidenefluorene (Va)[4] on being allowed to react with triphenylphosphine-*n*-butylidene (IIa) does indeed smoothly give the spiro compound IXa in addition to triphenylphosphine.




**Acknowledgments.**—We are indebted to Dr. R. E. Dean of the Coal Tar Research Association, Leeds, England, for a sample of spiro-(cyclopropane-1,9′-fluorene) (IXb).

## Experimental[12]

***n*-Butyltriphenylphosphonium Bromide.**—A solution containing 5 g. of triphenylphosphine and 15 cc. of *n*-butyl bromide in 5 cc. of benzene was boiled under reflux for 4 hr. and then cooled. The resulting precipitate was collected and washed with benzene. Crystallization from chloroform yielded 4.2 g. of the salt with m.p. 242–243°, reported[3] m.p. 235°.

*Anal.* Calcd. for $C_{22}H_{24}BrP$: Br, 20.02. Found: Br, 20.20.

**Spiro-(2,3-di-*n*-propylcyclopropane-1,9′-fluorene) (IXa).** (a) **From Fluorenone (I).**—A 1 *N* ethereal solution of butyllithium (9 cc.) was added to a suspension of 4 g. (10 millimoles) of *n*-butyltriphenylphosphonium bromide in 50 cc. of ether with swirling under nitrogen. The resulting deep red mixture was shaken in nitrogen for 2 hr. A solution of 0.6 g. (3.3 millimoles) of fluorenone in 15 cc. of ether was added, whereby a bulky white precipitate was formed which quickly turned brown-black. The mixture was shaken for 4 hr. and then allowed to stand overnight. Ether was distilled off at the same time as tetrahydrofuran was added until the distillation temperature reached 60°. The mixture was boiled under reflux for 6 hr., cooled, diluted with water and extracted with ether. The ether extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and then was dried and evaporated. Chromatography on 50 g. of alumina and elution with pentane gave 0.46 g. (50%) of the spiro compound IXa which after crystallization from ethanol showed m.p. 44–45°; $\lambda_{max}$ 227, 269, 292 and 303 mμ (log ε 4.33, 4.25, 3.99 and 4.06, respectively).

*Anal.* Calcd. for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 91.31, 91.45; H, 8.75, 8.71.

Further elution of the chromatogram with petroleum ether yielded 0.48 g. of triphenylphosphine and elution with ether gave 0.84 g. of triphenylphosphine oxide. Both these substances were identified by comparison with authentic samples.

(b) **From 9-*n*-Butylidenefluorene (Va).**—The reaction between 9-*n*-butylidenefluorene (Va)[4] (0.73 g., 3.3 millimoles) and triphenyl phosphine-*n*-butylidene was carried out exactly as described above, on the same scale. Chromatography on 50 g. of alumina and elution with pentane yielded 0.48 g. (52%) of the spiro compound IXa with m.p. 44–45°. Identity with a sample prepared by method a was established by mixture m.p. determination and infrared comparison. Further elution with petroleum ether gave 0.47 g. of triphenylphosphine. Elution with ether gave only 60 mg. of triphenylphosphine oxide.

**Oxidation of Spiro-(2,3-di-*n*-propylcyclopropane-1,9′-fluorene) (IXa) to Fluorenone (I).**—A solution containing

Handbook, 14th International Congress of Pure and Applied Chemistry, Zürich, July, 1955, p. 66; THIS JOURNAL, in press.

(9) H. Wieland and O. Probst, *Ann.*, **530**, 274 (1937).

(10) Although two isomers of structure IXa are possible, it was not determined whether the substance belongs to the *meso* or the racemic series.

(11) *Cf.* E. D. Bergmann, in "Progress in Organic Chemistry," Editor, J. W. Cook, Butterworths Scientific Publications, London, 1955, Vol. 3, pp. 107–109.

(12) Melting points are uncorrected. All chromatograms were made with Alcoa activated alumina, grade F-20 (Aluminum Co. of America, Pittsburgh, Pa.). Ultraviolet spectra were measured in 95% ethanol solution on a Unicam model S.P. 500 spectrophotometer. Analyses were carried out in our microanalytical laboratory under the direction of Mr Erich Meier.

200 mg. of the spiro compound IXa and 500 mg. of chromic acid in 5 cc. of glacial acetic acid was boiled under reflux for 2 hr. The mixture was cooled, diluted with water and the neutral product was isolated with ether in the usual way. Crystallization of the product from ethanol gave 65 mg. of fluorenone, m.p. 80–82°, undepressed on admixture with an authentic sample (m.p. 82–83°).

**Spiro-(cyclopropane-1,9′-fluorene) (IXb).**—A solution of triphenylphosphinemethylene was prepared by adding 24 cc. of a 1 *N* ethereal solution of butyllithium to a suspension of 8.9 g. (25 millimoles) of methyltriphenylphosphonium bromide[13] in 100 cc. of ether with swirling under nitrogen. The mixture was shaken for 2 hr., fluorenone (1.44 g.) in 25 cc. of ether was added and the reaction was then carried out exactly as described above. The product dissolved in benzene was filtered through 100 g. of alumina to remove triphenylphosphine oxide. The eluate was evaporated to dryness, dissolved in pentane and chromatographed on 100 g. of alumina. Elution with pentane and crystallization from methanol yielded 302 mg. of the spiro compound IXb, m.p. 50–55°. A sample, further purified by crystallization from methanol and high-vacuum sublimation, showed m.p. 68–70°; $\lambda_{max}$ 226, 268, 292 and 303 mμ (log ε 4.30, 4.20, 3.92 and 4.02, respectively). There was no depression in m.p. on admixture with an authentic specimen (m.p. 70–71°)[6] and the infrared spectra were identical.

Further elution of the column with petroleum ether (b.p. 65–70°) yielded 520 mg. of triphenylphosphine.

(13) G. Wittig and U. Schollkopf, *Ber.*, **87**, 1318 (1954).

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Polyphosphoric Acid as a Reagent in Organic Chemistry. IX.[1] Cyclization to Diaminoacridines[2]

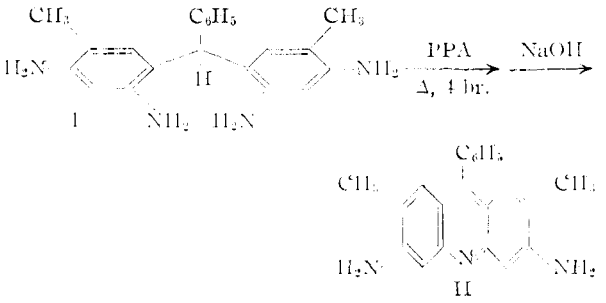
BY H. R. SNYDER AND MILTON S. KONECKY[3]

RECEIVED MARCH 7, 1958

In the presence of a little hydrogen chloride, tetraaminodiarylmethane derivatives such as I are cyclized and aromatized to diaminoacridine derivatives by polyphosphoric acid at 165°. The method appears superior to the usual two-step procedure for effecting this change. In an attempt to use *p*-toluenesulfonic acid in place of hydrogen chloride, di-*p*-tolyl sulfone was produced.

Since there is evidence that polyphosphoric acid acts as a cyclodeamination reagent,[4,5] its applicability to the synthesis of diaminoacridines by the cyclization of suitable tetramine precursors has been considered.

When the cyclization in polyphosphoric acid of the dihydrochloride salt of the tetraaminoditolylphenylmethane (I) was attempted, the diaminoacridine, benzoflavin (II), was obtained directly in reasonably good conversion (48%) and excellent




net yield (83%). The cyclization in polyphosphoric acid may constitute a better general method than that recorded in the literature.[6] The hot reaction melt is poured into cold water and the red phosphate salt of II precipitates. The acid salt is collected by filtration and treated with excess base; the free diaminoacridine base obtained is of excellent purity. Both cyclization and aromatization are accomplished in the polyphosphoric acid medium.

Since the heating of the dihydrochloride salt of I in polyphosphoric acid resulted in the generation of hydrogen chloride with concomitant foaming, the cyclization was repeated under the same conditions except that the free tetramine I was used. Surprisingly, the percentage conversion to benzoflavin (II) was only about one-half that obtained with the dihydrochloride. When hydrogen chloride was generated *in situ* by the periodic addition of solid sodium chloride to the tetramine I in polyphosphoric acid, the percentage conversion (33%) was intermediate between that obtained with the tetramine only and that obtained with the dihydrochloride salt.

It seemed likely that a non-volatile, strong acid would exert the same influence on the reaction as hydrogen chloride and, since it would not be removed from the reaction mixture, perhaps would be effective in catalytic quantities. However, when a mixture of *p*-toluenesulfonic acid and the tetramine I was heated in polyphosphoric acid, the conversion was lowered. The crude reaction product was a low-melting mixture from which *p,p′*-ditolyl sulfone and benzoflavin (II) were isolated with the aid of adsorption chromatography.

The isolation of the ditolyl sulfone suggested the possibility that polyphosphoric acid could be used as a reagent for the preparation of sulfones from sulfonic acids. A successful test of this supposition was accomplished when *p*-toluenesulfonic acid was heated in polyphosphoric acid under the same conditions as in the diaminoacridine cyclization and the sulfone was obtained in 28% yield.

In order to explore the scope of the cyclization in polyphosphoric acid to diaminoacridines, the syn

(1) For the preceding paper concerning cyclization with polyphosphoric acid see D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(2) Part of this work was supported by a grant [AT(11-1)-311] from the Atomic Energy Commission.

(3) Texas Co. Fellow, 1956–1957.

(4) H. Kissman, D. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952).

(5) C. Elston, Thesis, Doctor of Philosophy, University of Illinois, 1954.

(6) R. Meyer and R. Gross, *Ber.*, **32**, 2352 (1899).