Solvent Effects in Reactions of Phenylcyclopropyl Phenyl Ketones with Phosphorus Pentachloride[1,2]

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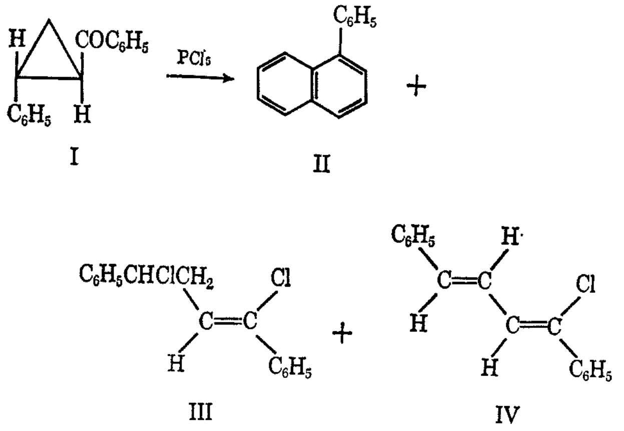
Reactions of *trans*-2-phenylcyclopropyl phenyl ketone (I) with phosphorus pentachloride in methylene chloride, carbon tetrachloride, chloroform, trichloroethylene, and nitroethane yield 1-phenylnaphthalene (II), *trans*-1,4-dichloro-1,4-diphenyl-1-butene (III), and *trans,trans*-1-chloro-1,4-diphenyl-1,3-butadiene (IV) in yields which vary with solvent. The *cis* isomer V gives similar results in methylene chloride and carbon tetrachloride. Reactions of 2,2-diphenylcyclopropyl phenyl ketone (VI) with phosphorus pentachloride in methylene chloride and carbon tetrachloride give 1,4-diphenylnaphthalene (X) and *trans*-1-chloro-1,4,4-triphenyl-1,3-butadiene (XI) in yields which vary with solvent. Possible mechanisms leading to the products are discussed.

Because of interest in the reactions of ketones with phosphorus pentachloride[3,4] we undertook further studies. In this paper the reactions of *cis*- and *trans*-2-phenylcyclopropyl phenyl ketones, *trans*-2-phenylcyclopropyl *p*-tolyl ketone, and of 2,2-diphenylcyclopropyl phenyl ketone with phosphorus pentachloride in different solvents are described.

The reactions of *trans*-2-phenylcyclopropyl phenyl ketone (I) (Scheme I) were studied in greatest detail. Three products, 1-phenylnaphthalene (II), *trans*-1,4-dichloro-1,4-diphenyl-1-butene (III), and *trans,trans*-1-chloro-1,4-diphenyl-1,3-butadiene (IV) were formed in amounts which varied with the solvent and the time of reaction. Occasionally, small amounts (2–3%) of *cis*-2-phenylcyclopropyl phenyl ketone (V) were also observed. The significance of this result will be discussed later. The reactions of *cis*-2-phenylcyclopropyl phenyl ketone (V) with phosphorus pentachloride in methylene chloride and carbon tetrachloride were similar to those of I. The results are summarized in Table I.

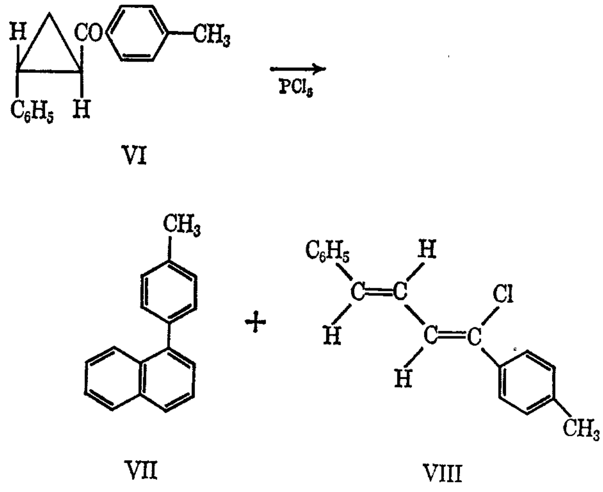
SCHEME I



The reactions listed in Table I were run several times with variations of time and concentration of reagents, except for those involving ketones V and VI. In general little variation from the yields reported were noted. The main solvent effect was that in carbon tetrachloride the rate of reaction was markedly less and very little 1-phenylnaphthalene (II) was produced.

The modest yields of 1-phenylnaphthalene (II) obtained in methylene chloride and nitroethane (expt 1 and 6, Table I) make this reaction of synthetic interest. Also, if one considers that whatever III (see Experimental Section for structure proofs of III and IV) is formed can be readily converted into IV by chromatography over alumina or treatment with base, the synthetic utility for formation of compounds similar to IV is apparent.

In order to prove which phenyl group in I was involved in the formation of the naphthalene nucleus in II, *trans*-2-phenylcyclopropyl *p*-tolyl ketone (VI) was prepared and treated with phosphorus pentachloride in methylene chloride and carbon tetrachloride (expt 9, Table I) to yield 31% of 1-*p*-tolylnaphthalene (VII).[5] By analogy this experiment indicates that the phenyl group on the cyclopropyl ring of I is the one which produces the naphthalene nucleus in II. Presumably the same phenyl group in the *cis* isomer V is involved in the formation of the naphthalene nucleus in II, although we did not prepare the analogous *cis*-*p*-tolyl ketone to check this point.



The reactions of 2,2-diphenylcyclopropylphenyl ketone (IX) with phosphorus pentachloride were studied in carbon tetrachloride and in methylene chloride. The products were 1,4-diphenylnaphthalene (X), *trans*-1-chloro-1,4,4-triphenyl-1,3-butadiene (XI), and *cis*-1-chloro-1,4,4-triphenyl-1,3-butadiene (XII). The struc-

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[1] The material in this paper was taken from the Ph.D. thesis presented by B. Ream to The Ohio State University, 1965.

[2] This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research Grant N. AF-AROSR-569-64.

[3] M. S. Newman, G. Fraenkel and W. N. Kirn, *J. Org. Chem.*, **28**, 1851 (1963).

[4] M. S. Newman and G. Kaugars, *ibid.*, **30**, 3105 (1965); **31**, 3179 (1966), and references therein.

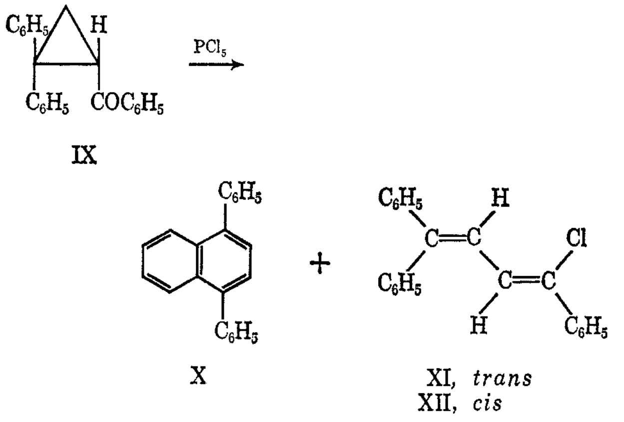
[5] A. Ohta, Y. Ogihara, K. Nei and S. Shibata [*Chem. Phar. Bull.* Tokyo), **11**, 754 (1963)] reported mp 52–54° for VII.

TABLE I

REACTIONS OF PHENYLCYCLOPROPYL KETONES I, V, AND VI WITH PHOSPHORUS PENTACHLORIDE

Expt	M^a Ketone	M^a PCl_5	Solvent	Temp,[b] °C	Time, hr	% recovery[c] Ketone	II (VII)	III	IV (VIII)
1	0.20[d]	0.28	CH_2Cl_2[e]	30	24	4	22	13	54
2	0.20[d]	0.28	CCl_4[e]	30	24	83	. . .	. . .	17
3	0.20[d]	0.26	CCl_4[f]	78	24	5	2	18	71
4	0.20[d]	0.28	$CHCl_3$[f]	60	30	23	2	15	46
5	0.20[d]	0.28	$Cl_2C{=}CHCl$[f]	86	24	3	4	13	72
6	0.20[d]	0.28	$CH_3CH_2NO_2$[f]	30	20	. . .	30	26	44
7	0.14[g]	0.15	CH_2Cl_2[e]	30	24	21[h]	21	15	32
8	0.20[g]	0.28	CCl_4[e]	78	45	12	7	18	56
9	0.25[i]	0.35	CH_2Cl_2[e]	30	44	10	31[j]	. .	38[k]
10	0.20[i]	0.28	CCl_4[f]	78	30	14	4[j]	. .	66[k]

[a] The molarity refers to the concentration of reactant in the reaction mixture after mixing reactants. [b] Reactions listed at 30° were run at room temperature and were magnetically stirred. [c] The percentages mean relative per cent of volatile products determined by glpc analysis on undistilled reaction products. When the percentages do not add up to 100% the remainder was due to one or more unidentified volatile products. The over-all isolated yields in most runs were high. [d] The ketone used was I. [e] In these experiments not all of the PCl_5 was in solution at the start. However, the PCl_5 soon (5–10 min) dissolved when ketone was added. [f] In these experiments the PCl_5 was dissolved in the solvent before the ketone solution was added. [g] The ketone used was V. [h] The ratio of I:V in this recovered ketone was 10:1. [i] The ketone used was VI. [j] VII. [k] VIII.



IX

X

XI, *trans*
XII, *cis*

tures of XI and XII were assigned mainly on the basis of the ultraviolet absorption spectra (see Experimental Section). The results are summarized in Table II.

TABLE II

REACTIONS OF 2,2-DIPHENYLCYCLOPROPYL PHENYL KETONE (IX) WITH PHOSPHOROUS PENTACHLORIDE

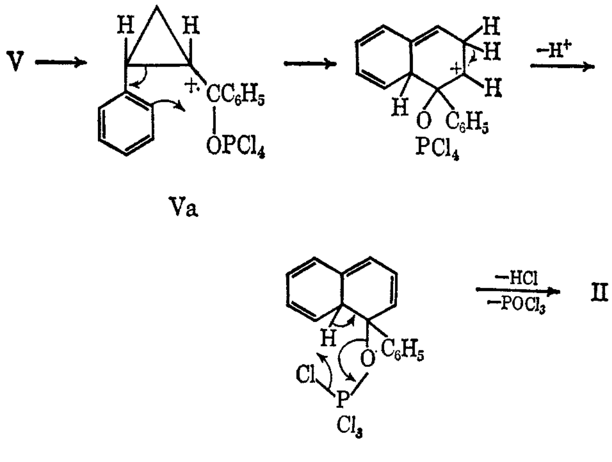
Expt	Solvent[a]	Temp, °C	Time, hr	%[b] IX	X	XI	XII
1	CH_2Cl_2[c]	30	18	. .	50	46	4
2	CCl_4	30	30	17	20	56	7
3	CCl_4	78	6	2	10	88	. .

[a] In all experiments the molarity of IX and PCl_5 were 0.20 and 0.28 *M*, respectively. [b] Relative percentages determined by glpc analysis on undistilled reaction products. In general the over-all yields were high. [c] In these experiments not all of the PCl_5 was in solution at the start. However, the PCl_5 soon (5–10 min) went into solution when the ketone was added. [d] In these experiments the PCl_5 was dissolved in the hot solvent before addition of the ketone solution.

The experiments in Table II show mainly that the formation of 1,4-diphenylnaphthalene (X) occurs more readily in methylene chloride than in carbon tetrachloride, to a greater extent in both solvents than the comparable formation of 1-phenylnaphthalene (II) from I, and more rapidly than the conversion of I to II in methylene chloride (*cf.* expt 1, Table II, with expt 1, Table I). In general the rate of reaction of IX is greater than that of I under comparable conditions.

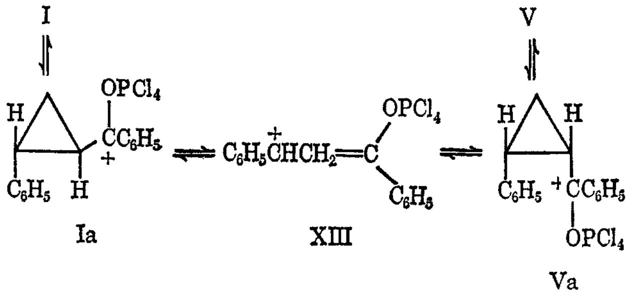
The most novel feature of the reactions described above is the new synthesis of substituted naphthalenes involved. Since 1-phenylnaphthalene (II) is obtained both from *cis* and *trans* ketones V and I and 1-*p*-tolylnaphthalene (VII) is obtained from VI, we believe that there must be a route by which I is converted to Va and that II is formed from Va by a succession of steps as shown in Scheme II.

SCHEME II



The formation of Va from I begins by the reaction of I with phosphorus pentachloride to form Ia by a step discussed previously,[6] followed by ring opening to the homoallylic cation XIII. The latter then cyclizes to the cyclopropylcarbinyl cation Va. Each of these steps is reversible as shown in Scheme III.

SCHEME III



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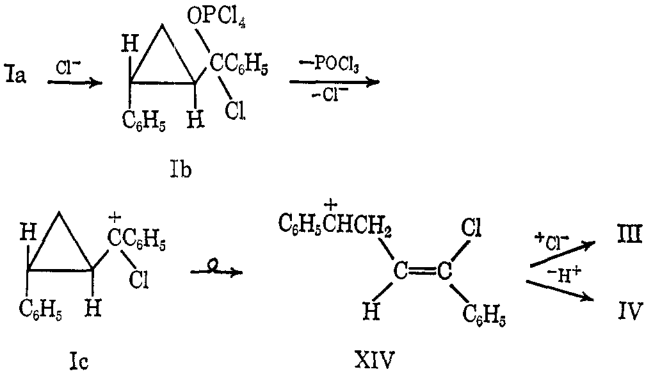
[6] M. S. Newman and L. L. Wood, *J. Org. Chem.*, **23**, 1236 (1958).

We believe that the formation of compounds III and IV proceeds through the chlorocarbonium ion[6] Ic formed *via* Ib from Ia. The chlorocarbonium ion Ic then isomerizes to the homoallylic cation XIV which yields III by taking on a chloride ion and IV by loss of a proton, as shown in Scheme IV. Interestingly, products of the same stereochemistry are formed from I and V.

SCHEME IV



It is possible to write a similar sequence for the formation of III and IV from Va; however, the addition of a chloride ion from some source to Va seems unlikely owing to steric hindrance. Rather Va would be expected to yield II or to isomerize to XIII. Indeed, the conversion of V to I has been effected by heating in carbon tetrachloride with hydrogen chloride and phosphorus oxychloride.

The effect of solvent on the rate of reaction and on the proportions of products formed is of interest. In this connection work of Professor S. Shore and his students on the nature of phosphorus pentachloride in different solvents may be of help.[7] Since extremely subtle effects must be invoked to explain the differences in rate of reaction and proportion of products when reactions are run in methylene chloride and carbon tetrachloride, discussion of solvent effects on these reactions will be deferred until more experimental work has been done.

The reactions of IX may be explained by paths comparable with those described above.

Experimental Section[8]

trans-2-**Phenylcyclopropyl Phenyl Ketone** (**I**).—This ketone was obtained[9] in 72% yielded in a 0.36-mole run as colorless crystals, mp 32–35°, near-infrared absorption[10] at 1.631 μ (0.449).

Reactions of I with PCl$_5$.—In a typical reaction a solution of 30.0 g (0.135 mole) of I in 250 ml of methylene chloride was added to a suspension of 31.3 g (0.15 mole) of PCl$_5$ in 250 ml of pure methylene chloride. After stirring at 30° for 68 hr the solvent was removed under reduced pressure and the residue was poured on ice. After extraction into ether and the usual work-up, removal of solvent left 42.6 g of oil shown[8] by glpc to contain I (5%), II (22%), III (20%), and IV (48%). After vacuum fractionation and chromatography of the lower boiling fraction, bp 131–134° (0.3 mm), over Woelm alumina (grade I) using Skellysolve B, there was obtained 2 g of pure 1-phenylnaphthalene as a viscous liquid which had the reported infrared[11] and ultraviolet[12] spectra, λ_{max}^{hexane} 224 mμ (ε 51,000) and 288 mμ (ε 8700).

Crystallization of a higher boiling fraction, bp 135–154° (0.3 mm), from Skellysolve B afforded 3.7 g of pure *trans,trans*-1-chloro-1,4-diphenyl-1,3-butadiene (IV): mp 114–115°; λ_{max}^{hexane} 233 mμ (ε 16,200), 328 (ε 58,900), and shoulder at 350 (ε 34,300).[13]

Anal. Calcd for $C_{16}H_{13}Cl$: C, 79.8; H, 5.5; Cl, 14.7. Found: C, 79.8; H, 5.4; Cl, 14.8.

We did not isolate pure III, but the evidence for its presence was as follows. To a solution containing 1.11 g of I and dry hydrogen chloride in CH_2Cl_2 was added 10 drops of POCl$_3$. After standing at 30° for 1 day, the usual work-up afforded 1.30 g of a yellow oil which glpc showed to be 90% one component and free of I. Crystallization from Skellysolve F afforded 0.80 g (62%) of 4-chloro-1,4-diphenyl-1-butanone, mp 87.5–89.0°, identical with an authentic sample[14] in melting point, infrared, and nmr spectra. A solution of 2.92 g of PCl$_5$ and 2.58 g of the above chloro ketone in 25 ml of CH_2Cl_2 was held at 30° for 1 day. After the usual work-up, there was obtained 3.0 g of an oil which on glpc analysis was composed of 8% of starting chloro ktone 57% of IV, and 31% of a compound assumed to be III. No II was present in this oil. When this mixture was chromatographed on neutral alumina hydrogen chloride was lost and there was obtained pure IV. Thus III had been converted into IV by this treatment. In another experiment, a mixture shown by glpc to contain 24% of II, 25% of III, and 51% of IV was hydrogenated in alcohol over platinum, a mixture was obtained which by glpc analysis consisted of 24% II and 76% 1,4-diphenylbutane. Pure IV was hydrogenated to pure 1,4-diphenylbutane in alcohol in the same way in 89% yield. The latter was isolated and shown to be identical with 1,4-diphenylbutane, mp 49–51°, prepared as described.[15] That the saturated chlorine was in the benzylic position was established by nmr analysis of a mixture of III and IV rich in III. Integration showed that only one benzylic hydrogen (τ 5.10, triplet, J = 7 cps) was present.

The other experiments listed in Table I were run in similar fashion and the products were analyzed by glpc.[8]

cis-2-**Phenylcyclopropyl Phenyl Ketone** (**V**).—Inactive *cis*-2-phenylcyclopropyl carboxylic acid was prepared as described[16] and converted by treatment with phenyllithium into V, mp 71.5–72.0°, near-infrared band at 1.629 μ (*c* 0.455), as described for the resolved acid.[17] After a solution of 0.5 g of V, dry hydrogen chloride, and POCl$_3$ in 5 ml of CCl$_4$ had been held at reflux for 1 day, isolation as usual yielded 0.5 g of an oil which

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[7] This work, which is being written for publication, shows that in carbon tetrachloride phosphorus pentachloride exists as a nonionic dimer, P_2Cl_{10}, where as in acetonitrile it exists as PCl_4^+, Cl^-. Studies on the nature of PCl$_5$ in other solvents are under way.

[8] All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The temperature was increased at a rate of 1°/min. Melting points for 2,4-dinitrophenylhydrazones are actually decomposition points. All analyses were done by MicroAnalysis, Inc., Wilmington, Del., unless otherwise noted. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Samples were dissolved in carbon tetrachloride, unless otherwise noted, and tetramethylsilane served as the internal standard. Near-infrared spectra were recorded on a Cary Model 14 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 spectrometer. The phrase "worked up in the usual manner" refers to the handling of organic solutions as follows. The solution was washed once with a saturated solution of sodium bicarbonate, with water, and then with a saturated sodium chloride solution, followed by filtration through anhydrous magnesium sulfate. Vapor phase chromatographic analyses were carried out on an F & M Model 609 flame ionization gas chromatograph, manufactured by the F & M Scientific Corp., Avondale, Pa. The unit was equipped with a Disc chart integrator and percentages of products were determined by integration of the areas under the peaks. A 2 ft × 0.25 in. stainless steel column, packed with 10% SE 30 silicone rubber on Chromosorb P, and at a temperature of 200–225°, was used for the analyses. Skellysolves are petroleum fractions designated as follows: Skellysolve F, bp 30–60°, Skellysolve B, bp 60–68°, Skellysolve C, bp 90–100°.

[9] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

[10] W. H. Washburn and M. J. Mahoney [*ibid.*, **80**, 504 (1958)] assigned the region 1.63–1.65 μ to cyclopropane CH stretching. P. G. Gassman [*Chem. Ind.* (London), 740 (1962)] found that 16 cyclopropane derivatives absorbed at 1.624–1.650 μ.

[11] We thank Dr. S. C. Dickerman, New York University, for an infrared spectrum of 1-phenylnaphthalene.

[12] R. A. Friedel and M. Orchin [*J. Am. Chem. Soc.*, **70**, 199 (1948)] reported $\lambda_{max}^{cyclohexane}$ 224 mμ (ε 56,200) and 286 mμ (ε 9300).

[13] F. Bergman, S. Israelashvili (Sarel), and D. Gottlieb [*J. Chem. Soc.*, 2522 (1952)] reported for 1,1,4-triphenyl-1,3-butadiene $\lambda_{max}^{95\%\ alcohol}$ 240 mμ (ε 19,900) and 335 mμ (ε 47,800).

[14] R. E. Lutz and J. S. Gillespie, Jr., *J. Am. Chem. Soc.*, **72**, 2002 (1950).

[15] E. E. Turner and F. W. Bury, *J. Chem. Soc.*, **123**, 2490 (1923).

[16] A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

[17] H. M. Walborsky and L. Plonsker [*ibid.*, **83**, 2138 (1961)] gave mp 63–67° for resolved ketone, and 69–70 for racemic ketone.

by glpc was shown to contain V and I in the ratio of 2:1. The presence of I in the mixture was checked by infrared bands at 7.68, 9.69, and 13.50 μ.

trans-**2-Phenylcyclopropyl *p*-Tolyl Ketone (VI).**—To a stirred suspension of 300 ml of dry dimethyl sulfoxide and 19.7 g (0.45 mole) of a 54.7% dispersion of sodium hydride in mineral oil under nitrogen was added 100 g (0.45 mole) of trimethylsulfoxonium iodide during 25 min.[9] After 1 hr the mixture was cooled to 22–24° and 95.9 g (0.43 mole) of benzal-*p*-methylacetophenone[18] in 150 ml of dimethyl sulfoxide was added during 45 min. After heating to 50° for 2 hr the cooled mixture was poured on ice and worked up as usual. Distillation afforded 93.4 g of VI as a yellow oil, bp 172–175° (0.3–0.4 mm). Crystallization from hexane yielded 91.0 g (90%) of VI: mp 47–48°; infrared bands at 1.632 μ (*c* 0.405, CCl_4), 6.02, and 9.72. Nmr analysis confirmed the assigned structure.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.3; H, 6.9.

The 2,4-dinitrophenylhydrazone, mp 233–235° dec, formed orange plates on crystallization from ethyl acetate.

Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.3; H, 4.8; N, 13.4. Found: C, 66.3; H, 4.8; N, 13.3.

Reactions of VI with PCl_5.—To a suspension of 14.6 g (0.07 mole) of PCl_5 in CH_2Cl_2 was added a solution of 11.8 g (0.05 mole) of VI in 100 ml of CH_2Cl_2. All of the PCl_5 was in solution within 15 min. After 44 hr at 30 ± 2° the solvent was removed under reduced pressure and the residue was treated with ice. The usual work-up yielded 14.2 g of an orange oil shown by glpc analysis to consist of 31% of 1-*p*-tolylnaphthalene (VII) 10% of VI, 21% of several minor unknown substances, and 38% of *trans,trans*-1-chloro-4-phenyl-1-*p*-tolyl-1,3-butadiene (VIII). A small amount of pure VII, mp 50–51.5°, was isolated from this mixture and shown to be identical with a sample of VII prepared in steps from α-tetralone and *p*-tolylmagnesium bromide[5] by mixture melting point, comparison of the ultraviolet spectra, λ_{max}^{hexane} 226 and 290 mμ (ε 55,000 and 11.400), and glpc retention time.

Chromatography of a part of the above orange oil over neutral alumina (Woelm grade I) afforded pure VIII as pale yellow plates: mp 112–113°; λ_{max}^{hexane} 237 mμ (ε 12,300), 328 (ε 54,700), and shoulder at 352 (ε 30,800). The nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{17}H_{15}Cl$: C, 80.1; H, 5.9; Cl, 13.9. Found: C, 80.0; H, 6.0; Cl, 13.9.

Reactions of 2,2-Diphenylcyclopropyl Phenyl Ketone (IX) with PCl_5.—To a suspension of 2.92 g (0.014 mole) of PCl_5 in 25 ml of CCl_4 was added 2.98 g (0.01 mole) of IX[19] in 25 ml of CCl_4. After holding at reflux for 4 hr, the solvent was removed under reduced pressure and the residue was treated with ice. After the usual work-up 3.4 g of a yellow oil was obtained which showed three peaks on glpc in the ratio 9:15:76. The first peak was shown to be starting ketone. The second peak (see below) was 1,4-diphenylnaphthalene (X). The third peak was *trans*-1-chloro-1,4,4-triphenyl-1,3-butadiene (XI) which was isolated by trituration of the oil with ethanol to yield 2.1 g of crystals. After two recrystallizations from Skellysolve B, 1.25 g (40%) of pure XI, mp 145–145.5°, $\lambda_{max}^{95\%\ C_2H_5OH}$ 249 mμ (ε 13,300) and 338 mμ (ε 38,400),[20] was obtained.

Anal. Calcd for $C_{22}H_{17}Cl$: C, 83.4; H, 5.4; Cl, 11.2. Found: C, 83.4; H, 5.3; Cl, 11.0.

On ozonolysis of 0.3 g of XI in 25 ml of CH_2Cl_2 at −78°, the neutral fraction was treated with 2,4-DPNH reagent. Recrystallization of the solid gave 0.12 g (39%) of orange-red benzophenone 2,4-dinitrophenylhydrazone, mp 244–245° dec. The infrared spectrum was identical with that of an authentic sample.[21]

In a similar experiment except that CH_2Cl_2 was the solvent, on mixing an exothermic reaction occurred for 2 min. The mixture was then allowed to stand at 30° for 18 hr (expt 1, Table II). Chromatography of the resulting oil using Skellysolve F-Skellysolve B, (1:1) afforded a fraction of almost pure X, which on crystallization from ethanol yielded X, mp 136.5–137.5°, alone and mixed with an authentic sample.[22] The ultraviolet spectrum in hexane showed peaks at 232 mμ (ε 49,400) and 301 mμ (ε 17,200)[23] and the nmr spectrum showed a complex at τ 2.12 (two protons) and 2.59 (14 protons).

No X was formed when a solution of 1,1,4-triphenyl-1-butene-4-one,[17] mp 126–127°, was refluxed in CCl_4 containing HCl and $POCl_3$.

Only a very small amount of compound XII, mp 110–111°, was isolated. We assume that it is the *cis* isomer of XI mainly because of an absorption maximum at 323 mμ (ε 43,000). The *trans* isomer XI absorbs at 338 mμ. In the 1,4-diphenyl-1,3-butadiene series, the *trans,trans* isomer absorbs at a longer wavelength than the *trans,cis* isomer.[24]

In addition to the peak at 323 mμ, XII also absorbs at 259 (ε 21,000) and at 230 (ε 33,000). Thus, our evidence for the structure of XII is incomplete but we did not spend more effort to isolate larger amounts in order to prove the structure.

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[18] A. D. Petrov and L. I. Anzus, *Ber.*, **66**, 4320 (1933).

[19] F. J. Impastato and H. M. Walborsky, *J. Am. Chem. Soc.*, **84**, 4838 (1962).

[20] Compare with spectrum for 1,1,4-triphenyl-1,3-butadiene.[18]

[21] R. L. Shriner, R. C. Fuson, and D. Y. Curtin ["The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p 318] reported mp 239°.

[22] We thank Professor E. Bergmann, Hebrew University, Israel, for an authentic sample of X. C. Dufraisse and R. Briou [*Bull. Soc. Chim. France*, [5] **5**, 502 (1938)] reported mp 135–136° for X.

[23] I. Gillet [*ibid.*, 1141 (1950)] gives λ_{max} at 302 mμ (ε 14,100) and end absorption with a cutoff at 250 mμ.

[24] J. H. Pinckard, B. Wille, and L. Zechmeister [*J. Am. Chem. Soc.*, **70** 1938 (1948)] gave λ_{max} 328 mμ (ε 55,500) for the *trans,trans* isomer and λ_{max} 315 mμ (ε 30,000) for the *trans,cis* isomer.

Sulfur-Containing Polypeptides. IV.
Synthetic Routes to Cysteine Peptides[1,2]

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Received November 23, 1965

Procedures for the incorporation of protected cysteine residues into peptide chains have been investigated and applied to the synthesis of two model hexapeptide derivatives. Methods for the selective removal of various protective groups have also been devised.

In several previous reports a number of aspects of the general problem associated with the synthesis of polypeptides cross-linked or looped at known positions by cystine residues have been considered. These have included studies on various sulfur,[1,5,6] nitrogen,[7] and carboxylic acid[7] protective groups and methods for the stepwise formation of two disulfide bonds within the same molecule.[8] Another important segment of

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[1] Part III of this series: R. G. Hiskey, T. Mizoguchi, and T. Inui, *J. Org. Chem.*, **31**, 1192 (1966).

[2] Supported by Grant A-3416 from the Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

[3] Abstracted in part from a dissertation by J. B. Adams, Jr., submitted to the University of North Carolina, Chapel Hill, in partial fulfillment of the requirements for the Ph.D. degree, June 1965.

[4] Shell Chemical Corp. Fellow, 1963–1964.

[5] R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4794 (1962).

[6] R. G. Hiskey, T. Mizoguchi, and H. Igeta, *J. Org. Chem.*, **31**, 1188 (1966).

[7] R. G. Hiskey and J. B. Adams, Jr., *J. Am. Chem. Soc.*, **87**, 3969 (1965).

[8] R. G. Hiskey and D. N. Harpp, *ibid.*, **87**, 3965 (1965).