Exchange Reactions of 4-Pyrone and 4-Pyrone Derivatives

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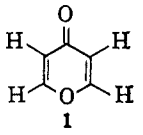
It has been established that the treatment of 4-pyrone under either neutral or acidic conditions with deuterium oxide produces 4-pyrone-3,5-d_2. Substitution of the ring protons with methyl groups deactivates the 4-pyrone ring to deuterium exchange. However, chelidonic acid has been found to exchange in the 3- and 5-positions, and has furnished an unambiguous method of preparing 4-pyrone-3,5-d_2. The mechanism of exchange probably proceeds by nucleophilic 1,4-addition–elimination to the pyrone system, possibly involving a ring-opened intermediate.

It was found by Lord and Phillips[1] that only *half* of the hydrogens of 4-pyrone (**1**) undergo reasonably rapid exchange with deuterium oxide at pH 7. They



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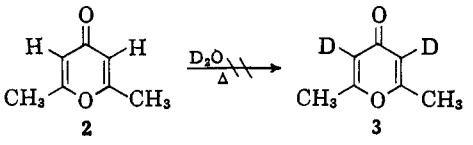
concluded that the exchange appeared to occur on the 2- and 6-carbons, from the fact that replacement of the hydrogens on these two positions with methyl groups to give **2** was found to inhibit the isotopic substitution. As it was mechanistically difficult to rationalize these results, we continued to investigate this problem and



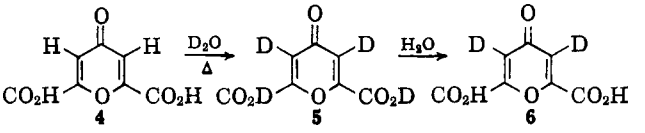
2 **3**

subsequently presented evidence which, in fact, supported isotopic exchange on the 4-pyrone ring system at the alternative positions (3 and 5).[2]

We now wish to present these results in detail and additional more recent data which conclusively support the assignment of the exchange-active sites on the 4-pyrone ring system to the 3- and 5-positions.

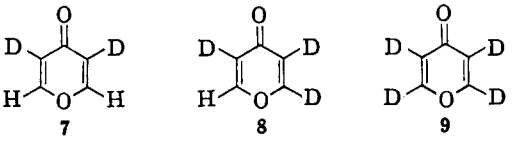
Following the initial studies with 2,6-dimethyl-4-pyrone (**2**),[1] exchange of this compound under more drastic conditions was investigated in an effort to overcome the inductive or possibly steric influence of the methyl substituents. The ring system, however, resisted isotopic substitution even when subjected to basic conditions which resulted in extensive decomposition.

It was then reasoned that if the 2,6-methyl groups affect the exchange primarily by an inductive effect and not by physically blocking the ring carbons, as was first supposed, one would expect chelidonic acid (**4**) to be at least as susceptible to exchange as the unsubstituted system, since the electron-withdrawing influence of the 2,6-carboxyl groups would tend to increase the sensitivity of the 4-pyrone ring system to nucleophilic attack. Isotopic substitution experiments in hot deuterium oxide demonstrated the ready conversion of chelidonic acid to 4-pyrone-3,5-d_2-2,6-



4 **5** **6**

dicarboxylic acid-d_2 (**5**). As would have been expected there was a large difference in exchange rates between the ring protons and the carboxyl groups. This rate difference was employed to achieve the preparation of 4-pyrone-3,5-d_2-2,6-dicarboxylic acid (**6**) by rapid recrystallization of the heavy acid from ordinary water. Decarboxylation of **6** should yield exclusively 4-pyrone-3,5-d_2 (**7**) and spectroscopic analysis of the product



7 **8** **9**

of decarboxylation did in fact reveal a preponderence of the isotopic derivative previously obtained by exchange of **1** with deuterium oxide.[1] The 4-pyrone-3,5-d_2 (**7**) was somewhat contaminated with an isotopic substitution product [4-pyrone-2,3,5-d_3 (**8**)] not obtained in the earlier exchange studies plus a measurable quantity of 4-pyrone-2,3,5,6-d_4 (**9**). These latter derivatives arose from incomplete exchange of the carboxyl groups during the rapid conversion of the heavy acid to the light acid. On the basis of these results it appeared that the role played by the methyl groups in inhibiting deuterium exchange in 2,6-dimethyl-4-pyrone (**2**) was of an inductive nature rather than direct blockage of these positions from attack.[2]

Exchange studies on 3-methyl-4-pyrone (**10**) which was synthesized according to the procedure of Willstätter and Pummerer[3] were also carried out to provide further evidence against direct exchange at the 2- and 6-positions. If exchange occurs at the 2- and 6-positions (**12**), two deuterium atoms would be incorporated during isotopic substitution of the 3-methyl derivative, but exchange only at the 5-position (**11**) is to be expected on the basis of the usually accepted addition–elimination mechanism. As the integrated extinction coefficient of the carbon–deuterium stretching band in the infrared spectrum is expected to be approximately one-half that of the carbon–hydrogen band, it was assumed that the exchange product would exhibit either a 1:1 or a 4:1 ratio of the areas of the

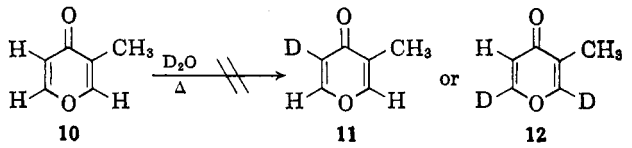
(1) R. C. Lord and W. D. Phillips, *J. Am. Chem. Soc.*, **74**, 2429 (1952).

(2) R. C. Lord, D. W. Mayo, and W. D. Phillips, *Anal. Chem.*, **26**, 429 (1954).

(3) R. Willstätter and R. Pummerer, *Ber.*, **38**, 1462 (1905).

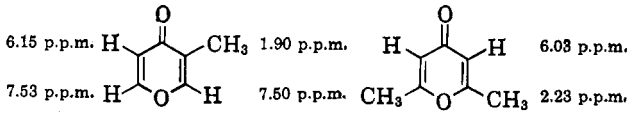
carbon–hydrogen and carbon–deuterium absorption bands.

The isotopic substitution studies with **10** gave no evidence of any deuterium incorporation after 26 hr. at 95°. This suggests that neuclophilic attack on



the 4-pyrone ring system is particularly sensitive to both inductive and hyperconjugative influence of the methyl substituents. The complete lack of exchange, however, in the case of 3-methyl-4-pyrone (**10**) provides further evidence that the methyl substituents do not function simply as blocking groups.

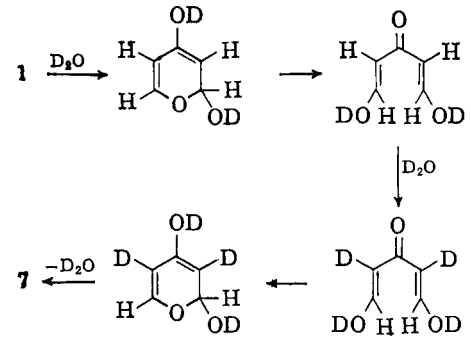
The synthesis of **10** also offers an opportunity to establish unambiguously the n.m.r. chemical shifts for the ring protons and from this information to ascertain without question the active positions of deuterium exchange on the 4-pyrone ring system. The n.m.r. spectrum of **10** in deuteriochloroform solution consists of three groups of resonances centered at δ = 7.52, 6.15, and 1.90 p.p.m. with areas in the ratio of 2:1:3. The resonance at high field is a singlet and may be assigned to the three 3-methyl protons. The resonance centered at δ = 6.15 p.p.m. is a doublet and is assigned to the proton bonded to the 5-carbon atom which is split (J = 6 c.p.s.) by coupling with the proton on the 6-carbon atom. The absorption found near δ = 7.52 p.p.m. consists of a doublet centered at δ = 7.53 p.p.m. which is assigned to the proton bonded to the 6-carbon atom split (J = 6 c.p.s.) by coupling with the proton on the 5-carbon atom, and a singlet, 7.50 p.p.m., which masks the high field leg of the doublet and which is assigned to the proton bonded to the 2-carbon atom.



The spectrum[4] of 2,6-dimethyl-4-pyrone (**2**), which possesses singlets centered at δ = 2.23 and 6.03 p.p.m., is consistent with these assignments. Moreover, they are also confirmed by recent work[5] on the n.m.r. spectrum of 4-pyrone which consists of two resonances of equal area centered near δ = 6.35 and 7.69 p.p.m. and assigned by Mathis and Goldstein[5] to the protons on the 3-carbon and 5-carbon atoms and the protons on the 2-carbon and 6-carbon atoms, respectively. An exchange carried out by us on 4-pyrone under essentially identical conditions with those previously reported[1] resulted in a large decrease (>50%) in the intensity of the high-field resonance compared with the low field multiplet and in the development of a strong singlet centered on top of the remains of the low-field multiplet. By utilizing all the above n.m.r. information, it is possible to assign unambiguously the structure of the isotopic substitution product as 4-pyrone-3,5-d_2 (**7**).

Finally, an examination of the n.m.r. spectrum of the mixture of isotopic compounds obtained earlier by the

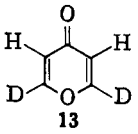
CHART I



decarboxylation of 4-pyrone-3,5-d_2-2,6-dicarboxylic acid (**6**) revealed that the proton-containing products were generated predominately (95%) with the proton attached to either the 2-carbon or the 6-carbon atom. This latter information substantiates the original interpretation of the isotopic substitution by infrared spectroscopy.[2]

We conclude that the mechanism of deuterium exchange on the 4-pyrone ring system probably involves nucleophilic addition–elimination to the α,β-unsaturated ketone system.[6] Although direct evidence has not been obtained in the present work[7], several nucleophilic reactions are known[3] in which the 4-pyrone ring system can be opened and reclosed, during which equilibration of the 3- and 5-positions can take place (see Chart I). Substitution of methyl groups on the ring, however, appears to deactivate the system both inductively and conjugatively, thereby inhibiting the isotopic exchange. Electron-withdrawing substituents, however, facilitate the deuterium exchange as evidenced by the ready formation of 4-pyrone-3,5-d_2-2,6-dicarboxylic acid-d_2 (**5**).

This latter compound can be used as a convenient source of 4-pyrone-2,3,5,6-d_4 (**9**) which in turn has been shown[1] to yield the difficult to prepare isotopic derivative, 4-pyrone-2,6-d_2 (**13**), on exchange with water. Since unambiguous assignments for the totally sym-



metric isotopic species are now available, the analysis of the infrared and Raman spectra of these compounds which were obtained earlier[8] is currently in progress and will be published elsewhere.

Experimental[9]

Attempted Preparation of 2,6-Dimethyl-4-pyrone-3,5-d_2 (3).—Several attempts were made to exchange the 3- and 5-hydrogens

(4) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962, p. 166.

(5) C. T. Mathis and J. H. Goldstein, *Spectrochim. Acta*, **20**, 871 (1964).

(6) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1958).

(7) See, however, P. Beak and G. A. Carls, *J. Org. Chem.*, **29**, 2678 (1964).

(8) W. D. Phillips, Ph.D. Dissertation, Massachusetts Institute of Technology, 1951.

(9) Melting points were observed in evacuated capillaries and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics and linear-frequency cam. Band centers are accurate to 3 cm.$^{-1}$ at wave numbers below 1500 cm.$^{-1}$. Spectra were recorded with pure liquid samples using a heated cell or with Nujol mulls. The proton magnetic resonance spectra were determined on a Varian A-60 spectrometer at a sweep width of 500 c.p.s. using deuteriochloroform solutions containing tetramethylsilane as an internal standard. The elemental analyses were carried out by Dr. S. M. Nagy and associates, Massachusetts Institute of Technology.

of **2** for deuteriums under basic conditions. A representative example of the procedure follows with additional experiments given in Table I. Sodium hydroxide (0.070 g., 0.0017 mole) was added to a solution of 2,6-dimethyl-4-pyrone (**2**)[10] (0.40 g., 0.0032 mole) in 99.8% deuterium oxide (7.0 g., 0.39 mole) and the basic solution which was protected from atmospheric moisture was heated for 14 hr. at 110°. During this period the solution turned a deep brown color and an amorphous solid precipitated. After removing the solvent *in vacuo*, **2** was recovered by recrystallization from carbon tetrachloride, m.p. 132°. Infrared analysis of the recovered material revealed no absorption in the C–D stretching region. It was estimated that about 1 atom % of deuterium could have been detected in the infrared spectrum.

TABLE I

EXCHANGE STUDIES WITH 2,6-DIMETHYL-4-PYRONE (**2**)[a]

$C_7H_8O_2$, moles	D_2O, moles	NaOH, moles	Time, hr.	Temp., °C.
0.0020	0.28	...	48	80
0.0032	0.39	0.0017	14	110
0.0060	0.53	0.0025	12	90
0.014	0.33	0.0023	12	90
0.014	0.58	0.0025	12	105

[a] No exchange was observed.

Preparation of 4-Pyrone-3,5-d_2-2,6-dicarboxylic Acid-d_2 (5).—Chelidonic acid[11] was recrystallized several times from water to give white needles, m.p. 256°. The final recrystallization of the acid was from 99.8% deuterium oxide and the sample was dried at 110° for 24 hr. in an atmosphere of dry nitrogen. The purified **4** (10.0 g., 0.054 mole) was dissolved in 99.8% deuterium oxide (150 g., 8.33 moles) in a closed system under a positive pressure of dry nitrogen. The solution which resulted was warmed for 72 hr. at 85°. At the end of this period the deuterium oxide was removed by vacuum distillation. This procedure was repeated once again and the residue obtained was dried for 4 hr. at 100° in a stream of dry nitrogen to give ~10.0 g. of 4-pyrone-3,5-d_2-2,6-dicarboxylic acid-d_2 (**5**). Infrared analysis of the residue revealed no absorption in the strongly bonded O–H stretching (3400–2400 cm.$^{-1}$) or the "C–H stretching" (3100 cm.$^{-1}$) regions of the spectrum.

Preparation of 4-Pyrone-3,5-d_2-2,6-dicarboxylic Acid (6).—The residue **5** (~10.0 g., 0.05 mole), after infrared analysis, was immediately treated with a mixture of 110 ml. of water and 10 ml. of concentrated hydrochloric acid. The addition of acid was used to help suppress exchange at the 3- and 5-positions.[1] The mixture was warmed to 95° for 10 min.[12] The reaction mixture was then cooled in an ice bath. A heavy cream-colored precipitate formed which was collected by rapid-suction filtration. The filter cake was washed with distilled water and dried *in vacuo* at 100° for 6 hr. to yield, ~8.0 g. (80% yield) of 4-pyrone-3,5-d_2-2,6-dicarboxylic acid (**6**). The infrared spectrum of **6** contained no absorption in the C–H stretching region; however, a portion of the original absorption band still appeared to persist in the bonded O–D stretching region.[12]

Preparation of 4-Pyrone-3,5-d_2 (7) by Decarboxylation of 4-Pyrone-3,5-d_2-2,6-dicarboxylic Acid (6).—In a drybox, 4-pyrone-3,5-d_2-2,6-dicarboxylic acid (**6**) (~8.0 g., 0.043 mole) was intimately ground with 25 g. of precipitated copper powder and transferred to a sublimation apparatus, where the mixture was heated in a dry nitrogen atmosphere. In the temperature range 265–280° a smooth evolution of gas occurred with simultaneous distillation of the crude product to yield 4.0 g. of greenish yellow **7**. Distillation of the crude material through a semimicro column *in vacuo* gave 3.5 g. (75% yield) of 4-pyrone-3,5-d_2 (**7**), m.p. 32.5°. The infrared spectrum of a neat sample was recorded. Bands were assigned to **7** and 4-pyrone-2,3,5,6-d_4 (**9**) by identification with peaks found in the spectra of samples previously obtained by direct synthesis and exchange.[1] Bands which did not correspond to peaks present in the spectra of the known compounds and bands with greater intensities than expected were attributed to the presence of 4-pyrone-2,3,5-d_3 (**8**). A semiquantitative indication of the isotopic species formed during the decarboxylation was obtained by consideration of the following peaks.

(1) A band of medium intensity found at 1112 cm.$^{-1}$ was shown to correspond closely to a peak identified in the spectrum of 4-pyrone-3,5-d_2 (**7**) near 1113 cm.$^{-1}$. The relative intensities of the two bands suggested the presence of approximately 60% **7** in the product mixture.

(2) A weak band located at 1140 cm.$^{-1}$ parallels a similar but very strong band near 1139 cm.$^{-1}$ in the spectrum of **9**. The intensity ratio of the two peaks indicates that the reaction product contains as much as 10% **9**.

(3) A band of medium intensity located near 892 cm.$^{-1}$ lacks correspondence with peaks in the spectra of the known isotopic derivatives. This peak can be attributed to, and also act as a measure of, the unsymmetrical isomer **8**.[13] As this species was the only other major component expected to be formed in the reaction, it was estimated by difference that the contribution of this material to the total sample could be as much as 20%.

(4) Since 4-pyrone-2,6-d_2 (**13**) possesses a strong peak near 1125 cm.$^{-1}$, lack of absorption in this region of the product spectrum was taken as evidence that very little **13** was formed during the decarboxylation.

The n.m.r. spectrum of a 635-mg. sample of the decarboxylation product in 0.1 ml. of carbon tetrachloride contained two sets of resonances centered near δ = 7.60 and 6.18 p.p.m. Integration showed that at least 95% of the hydrogens introduced during decarboxylation substituted on the 2- and 6-positions and that only a very small amount (~5%) of deuterium entered 2- or 6-positions which were adjacent to 3- or 5-positions substituted with hydrogen.[14]

Preparation of 3-Methyl-4-pyrone (10).—Alkylation of 4-pyrone (**1**) which had been synthesized by standard methods[15] was carried out by employing a procedure similar to that used by Willstätter[3] in which C-methylation of the ambident nucleophile was favored. To potassium methylate (0.05 mole) in 30 ml. of methanol in dry nitrogen atmosphere was added 4-pyrone (**1**) (4.8 g., 0.05 mole) and methyl iodide (7.5 g., 0.053 mole). The solution rapidly turned a bright yellow following addition of **1**. The reaction mixture was then held at 65° for 2 hr. At the end of this period the red solution was decanted from potassium iodide formed during the reaction and fractionally distilled. A fraction collected between 108 and 113° (12 mm.) was recrystallized from ligroin to give 0.79 g. (15% yield) of 3-methyl-4-pyrone (**10**), m.p. 67–68°.

Anal. Calcd. for $C_6H_6O_2$: C, 65.40; H, 5.51. Found: C, 65.39; H, 5.61.

The infrared spectrum of a liquid sample showed strong absorption at 1665 (C=O) and 1627 (C=C) cm.$^{-1}$, plus weak bands at 3100 (=C—H) and 2950 (CH_3) cm.$^{-1}$. The n.m.r. spectrum obtained in deuteriochloroform showed a singlet at δ = 1.90 p.p.m. (relative area 3) assigned to the methyl protons; a doublet at δ = 6.15 p.p.m. (relative area 1) assigned to H-5; and a multiplet at δ = 7.52 p.p.m. (relative area 2) assigned to H-2 and H-6.

Attempted Deuterium Exchange of 3-Methyl-4-pyrone (10).—A solution of 3-methyl-4-pyrone (0.2 g., 0.0018 mole) in deuterium oxide (0.2 g., 0.02 mole) was protected from atmospheric moisture and heated at 95° for 26 hr. Vacuum distillation of the reaction mixture afforded 0.16 g. (80% yield) of **10**, m.p. 67–68°.

(10) J. N. Collie and T. Tickle, *J. Chem. Soc.*, **75**, 710 (1899).

(11) E. R. Riegel and F. Zwilgmeyer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943 p. 126.

(12) Although incomplete dissolution occurred under these conditions, it was decided not to add further solvent or raise the exchange temperature. As a result of these decisions the exchange was approximately 80% complete (by infrared analysis of both the exchanged acid and the decarboxylation product).

(13) The chance that this peak arises from either a monodeuterium derivative or the 4-pyrone-2,3,6-d_3 derivative was considered to be a rather remote possibility because of the incomplete equilibration of the carboxyl groups.

(14) Owing to the fact that the decarboxylation sample had been stored for several years in an unsealed vial before the n.m.r. spectra were obtained, approximately 15% back exchange had occurred to produce a comparable quantity of 2,3- and 5,6-hydrogen-substituted sites which were not observed in the infrared spectra of the original sample. This back exchange would also be expected to increase the per cent of 2(D),3(H)- and 5(H),6(D)-substituted positions because of the presence of **8** and **9** as impurities. Thus, it is quite probable that our estimate of the extent of scrambling (~5%) is high and the decarboxylation gives exclusive substitution at the 2- and 6-positions.

(15) M. R. Cornubert and P. Robinet, *Bull. soc. chim. France*, **53**, 565 (1933).

Infrared analysis of the product showed no absorption in the C–D stretching region (~2290 cm.$^{-1}$). Two earlier attempts were made to induce exchange of the ring protons of **10** under milder conditions (70° for 10 hr., 90° for 24 hr.).

Preparation of 4-Pyrone-3,5-d_2 (7) by Exchange[1].—4-Pyrone (**1**) (1.82 g., 0.022 mole) and ~90% deuterium oxide (7.13 g., 0.36 mole) were heated together in a 50-ml. flask fitted with a reflux condenser and protected by a calcium chloride drying tube on an oil bath at 95° for 19 hr. The exchanged pyrone was then separated from the solvent by vacuum distillation. The infrared spectrum of the product showed absorption in both the C–H stretching region (3084 cm.$^{-1}$) and in the C–D stretching region (2289 cm.$^{-1}$). An n.m.r. spectrum of the partially deuterated material showed a large singlet at δ = 7.60 p.p.m. superimposed on the remains of a doublet at δ = 7.58 p.p.m. and a weak high field doublet at δ = 6.18 p.p.m. Integration indicated that the exchange was nearly 60% complete at this stage.

Acknowledgment.—We wish to thank the Smith, Kline and French Laboratories for a grant which supported part of this investigation.

Selective Friedel–Crafts Reactions. II.[1a] Alkylation of Olefins and Vinylbenzenes with α-Haloalkylbenzenes

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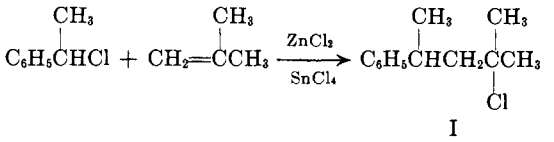
Olefins and vinylbenzenes react with α-haloalkylbenzenes in the presence of weak Friedel–Crafts catalysts such as $ZnCl_2$ or $SnCl_4$ by addition of the haloalkylbenzenes onto the olefinic double bond and not through alkylation of the aromatic ring. Subsequent dehydrohalogenation allows the preparation of α-aralkylated olefins or vinylbenzenes with high yields.

Lewis acid halide catalyzed addition of haloalkanes onto halo olefins have been first investigated by Boeseken and Prins.[2] The so-called Prins reaction has been applied by many other investigators for reactions of polyhaloalkanes with alkenes. It was, however, generally considered that mono- or polyhaloalkanes cannot be added by this reaction to simple olefins. It was Schmerling[3] who in a series of investigations studied the interaction of haloalkanes and olefins and arrived at the conclusion that in the presence of aluminum chloride and a number of less active Lewis acid halides the addition of haloalkanes onto olefins can be carried out with very satisfactory results.

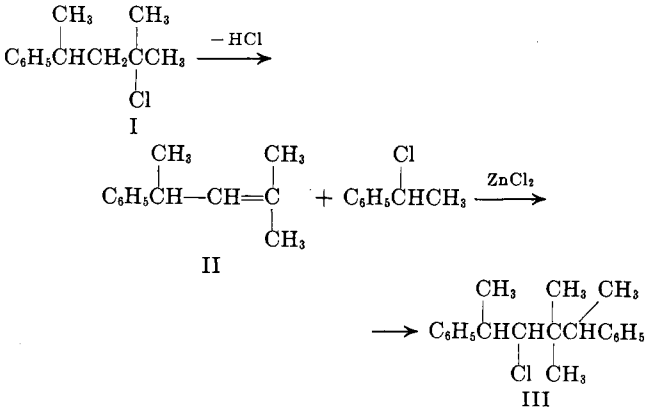
At the time of our investigations no data were available from the literature on the behavior of haloaralkanes with olefins other than indicating usual ring alkylations complicated by side reactions due to dehydrohalogenation of the haloalkane. After our work was disclosed in the patent literature,[4] a paper appeared by Paushkin and Mirgaleev[5] in which the interaction of α-chloroethylbenzene with propylene in the presence of $H_3PO_3 \cdot BF_3$ has been described producing unexpectedly 2-chloro-2-phenyl-3-methylbutane instead of 2-phenyl-4-chloropentane as was obtained in our work.[4]

Results and Discussion

While attempting to ring alkylate α-haloalkylbenzenes with olefins in the presence of Friedel–Crafts catalysts, we have observed that strong acid catalyst such as sulfuric acid or aluminum halides cause dehydrohalogenation and subsequent polymerization of the α-haloalkylbenzene instead of ring alkylation. Weaker catalysts, such as zinc and stannic halides do not catalyze ring alkylation of the α-haloalkylbenzene with olefins, but addition of the α-haloalkylbenzene onto the olefins takes place, as is illustrated in the reaction of α-chloroethylbenzene with isobutylene yielding 2-methyl-2-chloro-4-phenylpentane (I).



It has been observed that even if the reaction temperature is kept as low as 30° the haloalkylbenzene I formed loses, at least partially, HCl to form the corresponding olefin II, which then could react with excess α-haloalkylbenzene present to form III and the reaction can proceed accordingly to yield higher alkylates.



The α-haloalkylbenzenes usable in the present reaction include substituted α-haloethylbenzenes, α-chlorocumene, α-chloro-*n*-propylbenzene, α-chloro-*n*-butylbenzene, etc. Benzyl chloride failed to give the reaction. Suitable olefins in the reaction are alkenes containing at least three carbon atoms such as propylene, butenes, pentenes, hexenes, octenes, diisobutylene, styrene, vinyltoluene, etc. Zinc halides have been

(1) (a) Part I: G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **29**, 2317 (1964). (b) To whom correspondence should be addressed at The Dow Chemical Co., Eastern Research Laboratory, Framingham, Mass.

(2) J. Boeseken and H. J. Prins, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **13**, 685 (1911); **19**, 776 (1911).

(3) L. Schmerling, *J. Am. Chem. Soc.*, **67**, 1152 (1954); **68**, 1650, 1655 (1946); **69**, 1121 (1947); **71**, 753 (1949); **74**, 2855, 3592 (1952).

(4) G. A. Olah, S. J. Kuhn, and D. G. Barnes (to The Dow Chemical Co.), U. S. Patent 2,996,554 (1961).

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