

## Reaction of Inorganic Cyanates with Organic Halides.

## I. Direct Synthesis of Urethans

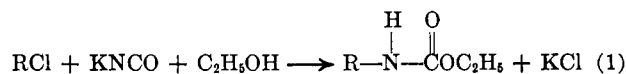
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The reaction of organic chlorides with potassium cyanate and ethyl alcohol in dipolar aprotic media to give the corresponding N-substituted urethan has been studied in detail. The reaction appears to be quite general. Several new urethans were prepared. A kinetic study, using benzyl chloride, showed the reaction to be first order in chloride. The effect of alcohol concentration, chloride concentration, and solvent type on the rate and selectivity to urethan was investigated.

Until recently, the application of isocyanic acid<sup>2</sup> and its salts<sup>3-5</sup> in organic synthesis has received little attention.

Alkali metal cyanates react with alkyl halides to give either isocyanates<sup>6</sup> or isocyanurates<sup>7</sup> depending on the reaction conditions and solvent. The synthesis of urethans (albeit in low yield) from the reaction of alkyl halides with alkali metal cyanates and an alcohol was first demonstrated by Kaiser<sup>8</sup> and reinvestigated recently by Fukui.<sup>9</sup> In view of the latter work, we wish to report our findings on the reaction of organic chlorides with potassium cyanate and ethyl alcohol in dipolar aprotic media to yield N-substituted urethans (eq. 1).



**Kinetics.**—The reaction of benzyl chloride with potassium cyanate<sup>10</sup> in dimethylformamide (DMF) is first order in benzyl chloride both in the presence and absence of ethyl alcohol. The rate of reaction of the chloride and the rate of formation of N-benzylurethan were measured by gas chromatography. A typical rate curve is shown in Figure 1, where  $A_0$  is the initial v.p.c. area per cent of benzyl chloride and  $A$  is the v.p.c. area per cent of benzyl chloride at time,  $t$ . The relationship between v.p.c. area per cent and concentration is discussed in the Experimental Section. Owing to the low volatility of 1,3,5-tribenzyl isocyanurate (the trimer of benzyl isocyanate), it was not possible to measure its rate of formation by gas chromatography. The rate data at various temperatures and initial concentrations of benzyl chloride and ethyl alcohol are summarized in Table I. The displacement rate constants,  $k_D$ , cited in Table I were obtained by dividing the observed rate constants,  $k_O$ , by the maximum solubility of potassium cyanate in pure DMF. Since the effect of the initial concentrations of benzyl chloride and ethyl alcohol on the

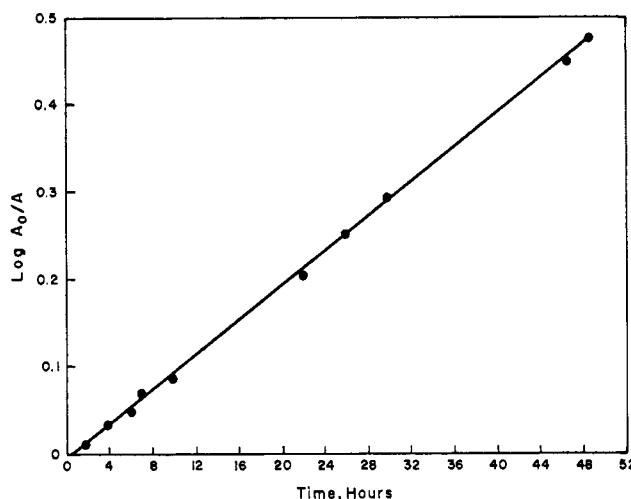


Figure 1.—A plot of  $\log (A_0/A)$  vs. time for the reaction of benzyl chloride (0.412  $M$ ) with  $\text{KNCO}$  and ethyl alcohol (1.775  $M$ ) in DMF at 50°.

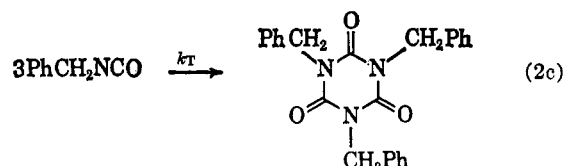
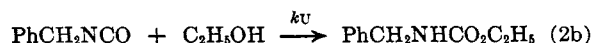
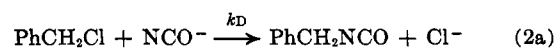
solubility of potassium cyanate has not been established, the absolute values of  $k_D$  are only approximate.

TABLE I  
EFFECT OF REACTANT CONCENTRATIONS AND TEMPERATURE ON RATE

Expt.	$[\text{C}_2\text{H}_5\text{OH}]_0$ , $M$	$[\text{PhCH}_2\text{Cl}]_0$ , $M$	Temp., °C.	$k_D^a \times 10^4$ , sec. <sup>-1</sup>
1	0.000	0.488	50.0	5.51
2	0.702	0.499	50.0	2.71
3	0.612	0.437	50.0	3.01
4	1.775	0.412	50.0	1.81
5	2.085	1.513	50.0	0.86
6	0.000	1.505	50.0	2.79
7	0.000	0.460	64.9	22.20
8	0.610	0.456	64.9	11.47
9	0.000	0.481	75.5	52.18
10	0.610	0.460	75.5	26.47

<sup>a</sup> The concentration (0.0354  $M$ ) of  $\text{KNCO}$  in all runs was assumed to be the same as in pure DMF.

The observed kinetic order is consistent with the following reaction sequence in which benzyl isocyanate



(1) To whom correspondence should be sent.

(2) See F. W. Hoover, H. B. Stevenson, and H. S. Rathrock, *J. Org. Chem.*, **28**, 1825 (1963), F. W. Hoover and H. S. Rathrock, *ibid.*, **28**, 2082 (1963), and **29**, 143 (1964), for example.

(3) A. Wurtz, *Ann.*, **71**, 326 (1849).

(4) H. K. Slotta and L. Lorenz, *Ber.*, **58**, 1320 (1925).

(5) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1595 (1940).

(6) C. M. Himmell (to Ethyl Corp.), U. S. Patent 2,866,801 (1958).

(7) K. Fukui and H. Kitano, U. S. Patent 3,037,979 (1962).

(8) D. W. Kaiser (to American Cyanamid), U. S. Patent 2,697,720 (1954).

(9) A. Nagasawa, H. Kitano, and K. Fukui, *Bull. Japan Petrol. Inst.*, **6**, 72 (1964).

(10) Owing to the low solubility (0.0354 mole/l.) of  $\text{KNCO}$  in DMF, its concentration throughout the reaction may be assumed constant. In the kinetic runs the initial concentration ratio,  $[\text{PhCH}_2\text{Cl}]_0/[\text{KNCO}]$ , ranged from 11 to 42.

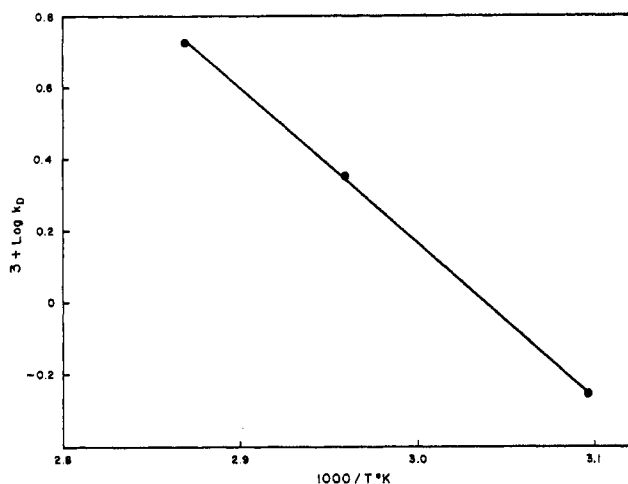


Figure 2.—Plot of  $\log k_D$  for the reaction of benzyl chloride with KNCO in the absence of ethyl alcohol vs. the reciprocal of the temperature ( $^{\circ}\text{K}$ ).

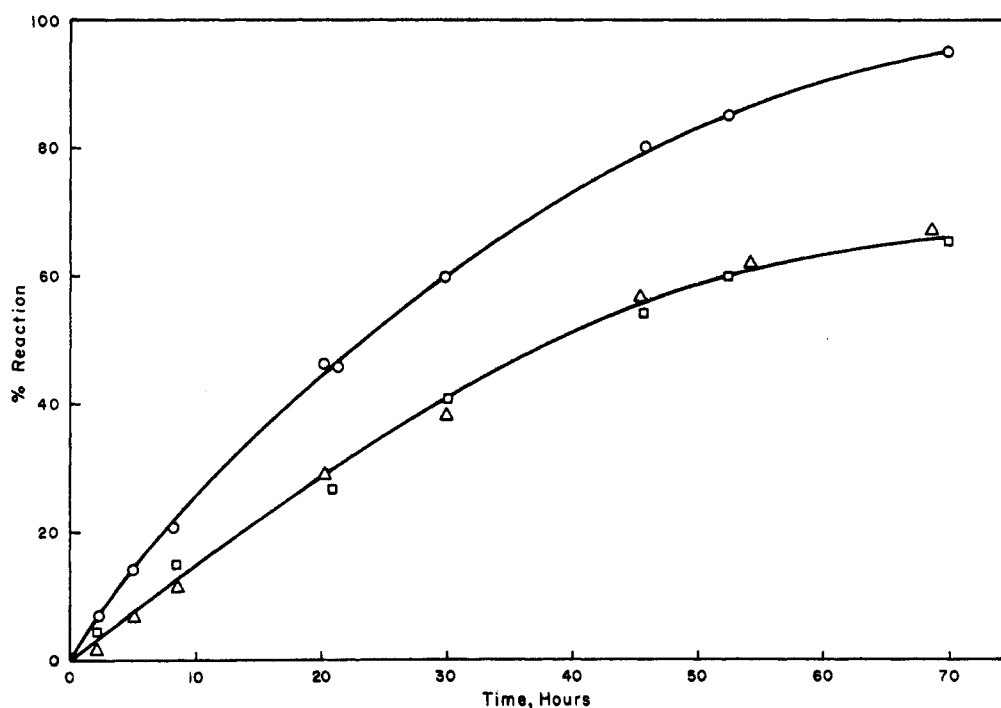


Figure 3.—Relationship of the rates of reaction of benzyl chloride (0.499  $M$ ) and ethyl alcohol (0.702  $M$ ) to the rate of formation of N-benzylurethan at  $50^{\circ}$ : O,  $\text{PhCH}_2\text{Cl}$ ; □,  $\text{C}_2\text{H}_5\text{OH}$ ; and Δ,  $\text{PhNHCO}_2\text{C}_2\text{H}_5$ .

is a reactive intermediate and  $k_U, k_T \gg k_D$ . This is reasonable in view of the facility with which isocyanates<sup>11</sup> react with alcohols at ambient temperatures.

An alternate displacement step involving attack of cyanate ion on a salt formed from benzyl chloride and DMF would lead to the same kinetic expression.

A plot (Figure 2) of  $\log k_D$  vs.  $1/T$  ( $^{\circ}\text{K}$ ) (from those runs carried out in the absence of ethyl alcohol) provided the following reaction parameters:  $E_a = 20.0$  kcal./mole,  $A = 1.9 \times 10^{10}$ ,  $\Delta H^* = 19.4$  kcal./mole at  $50^{\circ}$  and  $\Delta S^* = -13.7$  e.u. at  $50^{\circ}$ .

#### Effect of Ethyl Alcohol Concentration on Rate.—

The initial concentration of alcohol has little effect on the selectivity to urethan but does have a pronounced effect on the reaction rate. As shown in Table I, the rate of reaction of benzyl chloride diminishes with

increasing alcohol concentration. The retardation in rate is probably a consequence of altering the nature of the solvent system. It has been demonstrated in other systems<sup>12</sup> that protic compounds (*i.e.*, alcohols) detract from the unique solvent properties of dipolar-aprotic media (*e.g.*, DMF). Similarly, a rate decrease was observed on increasing the initial benzyl chloride concentration from 0.488 to 1.505  $M$  (Table I). This may be a consequence of two factors: (1) increasing the benzyl chloride concentration decreases the solubility of potassium cyanate, or (2) increasing the benzyl chloride concentration dilutes the effectiveness of the solvent system. In support of the latter argument, a slight but real deviation (rate acceleration) from first-order kinetics was observed in some of the rate experiments. This would be consistent with the fact that the relatively nonpolar benzyl chloride is continually being converted to a more polar substance (isocyanurate) which would detract to a lesser extent

from the solvent system. For this reason, the rate constants were derived from the first 10–30% of reaction.

**By-product Formation.**—While the displacement (step 2a) is rate controlling, the product distribution is governed by the relative rate at which benzyl isocyanate reacts with ethyl alcohol (step 2b) or trimerizes (step 2c) to isocyanurate. Since only step 2b requires ethyl alcohol in product formation, one would anticipate the selectivity to urethan to increase with increasing  $[\text{C}_2\text{H}_5\text{OH}]_0/[\text{PhCH}_2\text{Cl}]_0$ . As shown in Table II, the selectivity to urethan was essentially unaffected over the ratio range (1.4–4.3) studied.

To this point, it has been assumed that isocyanurate formation is the sole side reaction. This assumption is partially supported by isolation of the isocyanurate from several reaction mixtures. The possibility of

(11) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 61 (1957).

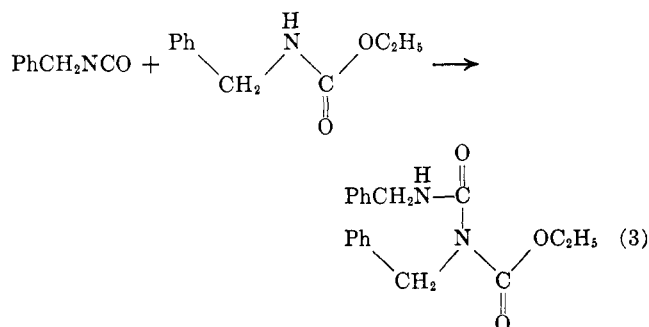
(12) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962).

TABLE II  
EFFECT OF  $[\text{C}_2\text{H}_5\text{OH}]_0/[\text{PhCH}_2\text{Cl}]_0$  ON SELECTIVITY  
TO BENZYLURETHAN

Expt.	$[\text{C}_2\text{H}_5\text{OH}]_0$ M	$[\text{C}_2\text{H}_5\text{OH}]_0/$ $[\text{PhCH}_2\text{Cl}]_0$	Temp., °C.	$k_D \times 10^4$ , sec. <sup>-1</sup> <sup>a</sup>	Selectivity <sup>b</sup>
2	0.702	1.406	50.0	2.71	0.66
4	1.775	4.315	50.0	1.81	0.64
3	0.612	1.400	50.0	3.01	0.64
5	2.085	1.377	50.0	0.86	0.63
9	0.610	1.377	64.9	11.47	0.61
11	0.610	1.327	75.5	26.47	0.62

<sup>a</sup> From the rate of disappearance of benzyl chloride. <sup>b</sup> Mole of urethane/mole of  $\text{PhCH}_2\text{Cl}$  reacted at one half-life.

allophanate formation (eq. 3) was rejected on the basis that the rate of urethan formation was found to be equal to the rate of ethyl alcohol consumption as shown in Figure 3. That is, if the product, benzylurethan, were competing with ethyl alcohol for reaction



with benzylisocyanate, the rate of alcohol consumption would exceed urethan formation. Since the allophanate is not sufficiently volatile to be detected by gas chromatography, all of the alcohol reacted would not be accounted for in terms of g.c. volatile products.

**Solvents.**—A number of solvents of varying structure were studied to determine their effect on the rate and selectivity to urethan in the reaction of benzyl chloride with potassium cyanate and ethyl alcohol. The results are summarized in Table III. It is curious

TABLE III  
EFFECT OF SOLVENT ON URETHAN FORMATION<sup>a</sup>

Expt.	Solvent <sup>b</sup>	$t_{1/2}$ , hr. <sup>c</sup>	Selectivity <sup>d</sup> to urethan
16	Dimethyl sulfoxide	0.25	0.13 (1.8 hr.)
11	Dimethylformamide <sup>e</sup>	1.90	0.57 (4.0 hr.)
17	N-Methylpyrrolidone	2.60	0.85 (23.5 hr.)
13	Acetonitrile	114	0.73 (114 hr.)
12	Ethanol	No reaction after 40 hr.	
14	Monoglyme	No reaction after 73 hr.	
15	Nitrobenzene	No reaction after 44 hr.	

<sup>a</sup> Initial benzyl chloride concentration, 0.845 M; initial ethanol concentration, 1.032 M; temperature, 75°. <sup>b</sup> KNCO was only slightly soluble in the solvents studied. <sup>c</sup> Time required for 50% of the benzyl chloride to be consumed. <sup>d</sup> Mole of N-benzylurethan formed/mole of benzyl chloride consumed after the time indicated in parentheses. <sup>e</sup> Initial benzyl chloride concentration, 0.460 M; initial ethanol concentration, 0.610 M.

that dimethyl sulfoxide (DMSO) provides the fastest rate but the lowest selectivity to urethan. The acceleration in rate is probably the result of the increased solubility of potassium cyanate in DMSO rather than a specific catalysis.<sup>13</sup> The low selectivity to urethan may

(13) J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961).

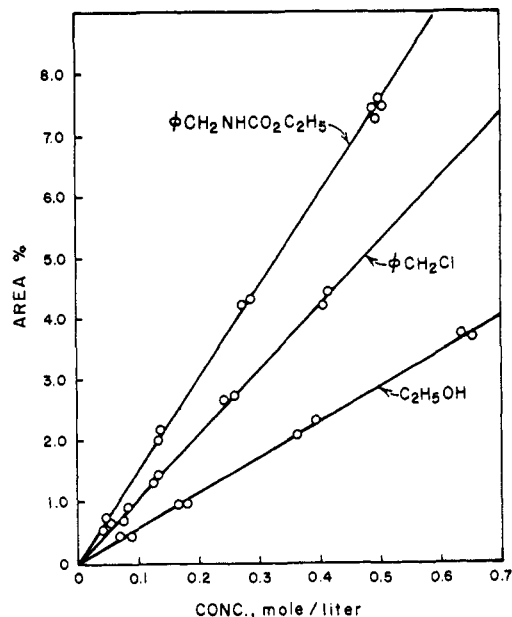
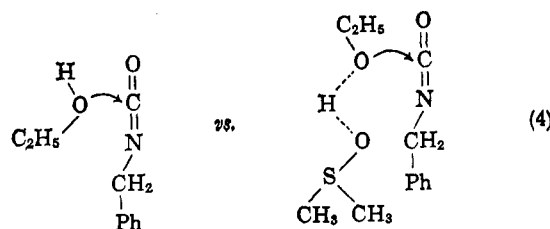


Figure 4.—Plot of g.c. area per cent (in relation to DMF) vs. concentration in mole/liter of reaction components.

be a result of two factors: (1) DMSO hydrogen bonds with the alcohol thereby reducing alcohol catalysis<sup>14</sup> in urethan formation, (2) the hydrogen-bonded complex of DMSO and the alcohol would be a poorer nucleophile (from steric considerations) than the "free alcohol" as compared in eq. 4.



It is interesting to note that nitrobenzene did not support reaction after 44 hr. but could be initiated by the addition of DMF (33 vol. %). The reaction was essentially complete after 98 hr. following the addition.

From the standpoint of both rate and selectivity, N-methylpyrrolidone appears to be the solvent of choice.

**Scope.**—The reaction of organic chlorides with cyanate ion using ethyl alcohol as the isocyanate trap to form urethans appears to be quite general. In Table IV are listed some of the chlorides studied and urethans obtained. The rough relative reactivities of the isomeric butyl chlorides (primary > secondary >> tertiary) are consistent with an  $\text{S}_\text{N}2$  process.

### Experimental Section<sup>15</sup>

**Materials.**—The DMF (Eastman Yellow Label) was purified prior to use by drying over calcium hydride and distilling *in vacuo* through an 86-cm. Vigreux column. The heart cut was em-

(14) W. G. P. Robertson and J. E. Stutchbury, *J. Chem. Soc.*, 4000 (1964).

(15) All melting points were taken in a Fisher-Johns hot stage melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer using KBr disks where applicable. Microanalyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo.

TABLE IV  
 SYNTHESIS OF URETHANS FROM ORGANIC CHLORIDES IN DMF

Expt.	Organic chloride	Temp., °C.	Time, hr.	KNCO/ RCl	Product	Yield, % <sup>a</sup>	M.p. and b.p. (mm.), °C., <sup>nd</sup> Lit.	Calcd., %			Found, %		
								C	H	N	C	H	N
18	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl	50	68	1.5	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et	73.3	41.5-42.0	67.00	7.26	7.82	66.76	7.19	7.89 <sup>e</sup>
19	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl	100	6	1.5	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et	88.8	48.9 <sup>b</sup>	...	...	...	...	...	...
20	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl	75	75	1.5	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et	9.8	202-203 (765), <sup>d</sup> 1.4282 (25)	...	...	...	...	...	...
21	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl	120	24	1.5	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et	77.6	87-88 (14), <sup>f</sup> 1.4276 <sup>e</sup>	...	...	...	...	...	...
22	CH <sub>3</sub> CH <sub>2</sub> -CH-CH <sub>3</sub>   Cl	120	46	1.5	CH <sub>3</sub> -CH <sub>2</sub> -CHNHCOC <sub>2</sub> H <sub>5</sub>	55.3	87-88 (14), <sup>f</sup> 1.4267 <sup>e</sup>	...	...	...	...	...	...
23	(CH <sub>3</sub> ) <sub>3</sub> CCl	120	92	1.5	EtO-C-NH <sub>2</sub> <sup>g</sup>    O	Low	45-46	40.44	7.92	15.72	40.33	8.11	15.71 <sup>e</sup>
24	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> Cl	100	45	1.5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et	76.1	33.6-34.3	...	...	...	...	...	...
25	1-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> Cl	100	21	1.5	1-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> NHCO <sub>2</sub> Et <sup>h</sup>	84.9	95-96	73.36	6.55	6.11	73.32	6.58	6.19
26	1,4-(ClCH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	100	19	2.5	1,4-(EtO <sub>2</sub> CNHCCH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>i</sup>	70.6	137-138	60.00	7.14	10.00	60.03	7.17	9.88
27	l-ClCH <sub>2</sub> CH=CHCH <sub>2</sub> Cl	100	4.5	2.5	EtO <sub>2</sub> CNHCCH=CH-CH=CHCH <sub>2</sub> NHCO <sub>2</sub> Et <sup>j</sup>	77.3	113.5-114.2	52.20	7.82	12.18	52.13	7.78	12.03
		60	64										

<sup>a</sup> Based on organic chloride charged. <sup>b</sup> W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1022 (1953). <sup>c</sup> Owing to the divergence in the melting points of these products with those reported in the literature, we felt it necessary to obtain elemental analyses. <sup>d</sup> E. A. Werner, *J. Chem. Soc.*, **115**, 1010 (1919). <sup>e</sup> J. W. Brühl, *Z. physik. Chem.*, **22**, 390 (1897). <sup>f</sup> C. S. Marvel and W. A. Noyes, *J. Am. Chem. Soc.*, **42**, 2259 (1920). <sup>g</sup> The anticipated product, N-*t*-butylurethan, was not present in the reaction mixture. <sup>h</sup> D. McCreath, *Chem. Ber.*, **8**, 384 (1875). <sup>i</sup> H. M. Curry and J. P. Mason, *J. Am. Chem. Soc.*, **73**, 5044 (1951). <sup>j</sup> To our knowledge, these compounds have not been reported in the literature.

employed in all runs. N-Methylpyrrolidone (Matheson Coleman and Bell) and dimethyl sulfoxide (Eastman Yellow Label) were purified in a similar manner. Benzyl chloride (Mallinckrodt, reagent grade) was distilled through a 43-cm. Vigreux column at 25 mm. and stored under dry nitrogen prior to use. Absolute ethanol (U. S. Industrial Chemical) was refluxed for 12 hr. over freshly ignited CaCO<sub>3</sub> and distilled prior to use. Potassium cyanate (J. T. Baker, reagent grade) was vacuum dried at 50°. The 1-(chloromethyl)naphthalene was purchased from Aldrich Chemicals and used as received. All other starting materials were Eastman (White Label grade) and were used as obtained from the manufacturer.

**Kinetic Procedure. Benzyl Chloride System.**—The apparatus consisted of a 100-ml. three-neck flask, equipped with a mechanical stirrer, rubber septum, condenser, and a bubbler to maintain a constant head of nitrogen. The reaction vessel was heated by means of a constant-temperature oil bath (±0.1°). Stock solutions containing the appropriate reactants in DMF were prepared and brought to temperature before addition of the dry KNCO powder. Samples were removed by hypodermic syringe, cooled to 0° in an ice bath, and analyzed by gas chromatography.<sup>16</sup>

**Kinetic Study.**—Assuming the displacement reaction (eq. 2a) to be rate controlling, the rate of reaction of benzyl chloride can be expressed by the rate expression given in eq. 5. Since the

$$-\frac{d[\text{PhCH}_2\text{Cl}]}{dt} = k_D[\text{PhCH}_2\text{Cl}][\text{KNCO}] \quad (5)$$

solubility of KNCO in DMF is very low and a stoichiometric excess based on the chloride was employed in all runs, the concentration of KNCO is assumed to be constant (0.0354 M) throughout the reaction.<sup>17</sup> The solubility of KNCO in mixtures of benzyl chloride, ethyl alcohol, benzylurethan, and DMF was not determined. The rate expression reduces to eq. 6

$$-\frac{d[\text{PhCH}_2\text{Cl}]}{dt} = k_D[\text{PhCH}_2\text{Cl}] \quad (6)$$

where  $[\text{KNCO}]k_D = k_0$  = the observed pseudo-first-order rate constant. Thus, the displacement rate constant,  $k_D$ , is obtained by dividing the observed rate constant,  $k_0$ , by the KNCO concentration.

In order to relate gas chromatographic area per cent to the concentration of the reactants and products, calibration curves (Figure 4) were obtained for benzyl chloride, ethyl alcohol, and benzylurethan in DMF. Since the molarities are a linear function of area per cent, eq. 7 is applicable.

$$-\int_{A_0\%}^{A\%} \frac{d[\text{PhCH}_2\text{Cl}]}{[\text{PhCH}_2\text{Cl}]} = k \int_0^t dt \quad (7)$$

**Scope.**—The following example is typical for the preparation of the urethans listed in Table IV. A slurry composed of 6.07 g. (75 mmoles) of KNCO, 3.9 g. (85 mmoles) of ethanol, and 40 ml. of DMF was heated at 100° with good stirring. Benzyl chloride (6.33 g., 50 mmoles) in 5 ml. of DMF was added dropwise and the resulting mixture heated an additional 6 hr. The salts were collected by filtration and the filtrate was vacuum distilled to remove unreacted starting material and solvent. The residue was triturated with ether and filtered. Slow evaporation of the ether afforded 6.2 g. (70% yield) of N-benzylurethan, m.p. 41.5-42.0° [from ether-petroleum ether (b.p. 20-40°)].

The infrared spectra of all the products showed strong absorption bands at 3350 (N-H), 1695-1730 (C=O), 1540 (C-N-H), and 1250 cm.<sup>-1</sup> (C-O) consistent with the urethan grouping.<sup>18</sup>

(16) The crude samples were analyzed on an F & M Model 720 dual column gas chromatograph. A 2 ft. × 0.25 in. column, packed with 15% UCON-50 HB-2000 (Union Carbide Chemicals) on Gas-Pack F, programmed from 50 to 200°, gave satisfactory results.

(17) The solubility of KNCO in DMF was determined at 50, 65, and 75°. KNCO was stirred at the given temperature for 1.5 hr. and the undissolved salt was allowed to settle to the bottom. A sample of the solution was removed and diluted to 100 ml. for analysis by flame photometry. A Beckman DU spectrometer with flame attachment was used for measuring potassium. at 766 μ. Molar concentration observed at all temperatures was 0.0354 M.

(18) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p. 266.

**Acknowledgment.**—The authors wish to thank Professors Charles De Puy and Melvin Hanna for editing this manuscript and acknowledge the assistance of Mr. James Harris and Mr. Dale Fox in performing

some of the final experiments. We are also indebted to Mr. David Conway for obtaining the infrared spectra and to Mrs. Frances Sims for her assistance in composing this manuscript.

## Synthesis of Ketones of the Type $\text{CH}_3\text{COCH}_2\text{R}$ from Acetylacetone and Halides with Ethanolic Potassium Carbonate. An Alkylation–Cleavage Process<sup>1</sup>

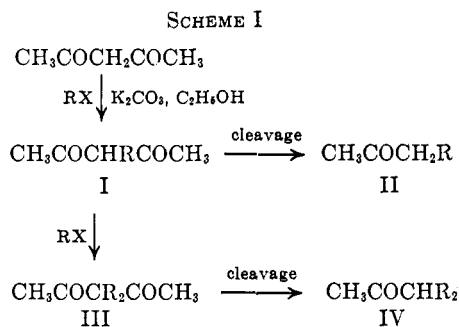
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A number of ketones of the type  $\text{CH}_3\text{COCH}_2\text{R}$ , where R is alkyl, aralkyl, or a related group, were prepared in good yield from acetylacetone and appropriate halides by means of ethanolic potassium carbonate. This alkylation–cleavage process appears more convenient than earlier procedures. Other courses of reaction were observed with certain halides. One of these involved dialkylation and cleavage to give the ketone of the type  $\text{CH}_3\text{COCHR}_2$ ; this process was useful when R was *m*-nitrobenzyl. Twofold monoalkylation and cleavage occurred with  $\alpha,\alpha'$ -dichloro-*p*-xylene to form 4,4'-phenylenedi-2-butanone.

It is well known that acetylacetone can be alkylated with an alkyl halide by means of a suitable base<sup>2</sup> and that the resulting alkyl derivative can be cleaved by an alcoholic base.<sup>3</sup> We have effected such an alkylation–cleavage process to form ketones of type II in a single procedure by means of ethanolic potassium carbonate; in certain cases a dialkylation–cleavage process to form ketones of type IV was also observed (Scheme I).



The general procedure involved refluxing approximately equal molecular equivalents of acetylacetone, halide, and potassium carbonate in ethanol for 16 hr.<sup>4</sup> The results with most of the halides studied are summarized in Tables I–III. Table I shows that the yields of ketones of type II were generally satisfactory (52–79%). The products on which the yields were based were indicated to be pure by v.p.c. or sharp melting point. This method is useful for the synthesis of a number of ketones II, especially those in which R is a substituted benzyl, a methallyl, or a phenacyl group. However, the reactions with *o*- and *p*-nitrobenzyl chloride afforded black mixtures, from which the corresponding ketones II were isolated only as their semicarbazones (see Table I and Experimental Section).<sup>5</sup>

(1) This investigation was supported by National Science Foundation Research Grant No. NSF GP 2274 and by Public Health Service Research Grant No. CA 04455-06.

(2) See A. W. Johnson, E. Markham, and R. Price, *Org. Syn.*, **42**, 75 (1962).

(3) See R. G. Pearson and E. A. Mayerle, *J. Am. Chem. Soc.*, **73**, 926 (1951).

(4) The reaction with *o*-chlorobenzyl chloride was mentioned without details in footnote 12 of a recent paper: T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **29**, 1391 (1964).

Six of the ketones II listed in Table I are known compounds; they were identified by infrared spectra (for the carbonyl group) and by essential agreement of their melting or boiling points and also of those of derivatives with the reported values.<sup>6</sup> The present one-stage procedure appears more convenient than the earlier, two-stage procedures involving alkylation of acetoacetic ester followed by cleavage,<sup>7</sup> and the Claisen–Schmidt condensation of acetone with the appropriate aldehyde followed by reduction of the resulting  $\alpha,\beta$ -unsaturated ketone<sup>8</sup> (see Table I). Also the present synthesis of II (R =  $\text{CH}_2\text{COC}_6\text{H}_5$ ) seems preferable to that involving the Friedel–Crafts acylation of benzene with levulinyl chloride.<sup>9</sup>

The other 10 ketones II listed in Table I appear to be new compounds. Their structures were supported by analyses (Table II) and by absorption spectra. The infrared spectra of all of the ketones showed the expected carbonyl absorption near  $5.85 \mu$ , and those of the nitro ketones also exhibited nitro absorptions near 6.5 and  $7.4 \mu$ <sup>10</sup> (see Table I). The n.m.r. spectra, which were determined on five of the new ketones II (Table III), showed the expected singlet for the methyl hydrogen and appropriate peaks for the aromatic hydrogens. The spectra of the *meta*- and *para*-substituted benzyl ketones II exhibited collapsed  $A_2B_2$  systems and that of *o*-bromobenzyl ketone II a complex  $A_2B_2$  system for the respective ethylene groups ( $-\text{CH}_2\text{CH}_2-$ ).

As indicated in Scheme I, intermediate I may undergo not only cleavage to form ketones II, but also further alkylation to give III which may be cleaved to afford ketones IV. The latter course of reaction apparently

(5) Although such alkylations have generally been assumed to involve an  $\text{S}_{\text{N}}2$  mechanism, a radical-anion process has been proposed recently for carbon alkylation of the anion of 2-nitropropane with *m*- and *p*-nitrobenzyl halides: R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, **86**, 3904 (1964).

(6) That II [R =  $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}_2$ ] had not isomerized to the possible  $\alpha,\beta$ -unsaturated ketone, 5-methyl-3-hexen-2-one, was further supported by the failure of its infrared spectrum to show a conjugated carbonyl (see Table I).

(7) See C. S. Marvel and F. D. Hager, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 243; J. R. Johnson and F. D. Hager, *ibid.*, p. 343.

(8) See N. L. Drake and P. Allen, Jr., ref. 7, p. 69; J. Frederick, J. Dippy, and R. L. Lewis, *Rec. trav. chim.*, **56**, 1000 (1937).

(9) J. H. Helberger, *Ann.*, **522**, 269 (1936).

(10) See L. J. Bellamy, "The Infrared Spectra of Complex Organic Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 298.