Organic Syntheses with Anion Exchange Resins. I. The Malonic Ester Synthesis and Related Reactions

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A quarternary ammonium hydroxide type of anion exchange resin, Amberlite IRA-400(OH$^-$), was found to be an effective catalyst for the alkylation of ethyl malonate, ethyl cyanoacetate, or cyanoacetamide with various alkyl halides. It was found that the resin (OH$^-$) rapidly exchanges its labile hydroxyl ion with the enolate of the active methylene compound even in aqueous solution producing the resin (R$^-$) which could subsequently react with alkyl halide to give the resin (X$^-$) and the desired alkylation product. The resin (R$^-$) was stable enough to isolate in the dry state.

Anion exchange resins have been shown to be excellent catalysts in various organic reactions such as cyanohydrin formation,[1] aldol condensation, and crotonization,[2-6] nitro alcohol formation,[1,7] or the various modifications of the Knoevenagel[2,9,10] and Michael condensations.[8,11-13] But the utilization of an anion exchange resin for the alkylation of active methylene group with alkyl halide has not been reported to date.

It has been found that a quarternary ammonium hydroxide type of anion exchange resin, Amberlite IRA-400(OH$^-$) is an effective catalyst for the alkylation of ethyl malonate, ethyl cyanoacetate, or cyanoacetamide with alkyl halides. The reaction product can be obtained by simple filtration of the solution away from the resin, and no neutralization or separation problems are required. Additionally, the resin can be readily regenerated by treating with dilute sodium hydroxide solution.

The reaction was generally carried out at room temperature with agitation of the reactants in the presence of a molar equivalent of Amberlite IRA-400(OH$^-$) in ethanol or ethanol–water solution depending on the solubility of the reactants employed. Fifty volume per cent ethanol–water was used as solvent with the runs of cyanoacetamide and its C-monosubstituted derivatives. The results of these experiments are summarized in Tables I and II. The analysis of the alkylated esters was achieved by gas chromatography. In the reaction of acetamidocyanoacetamide with allyl bromide, doubling the ratio of resin to reactants, raising the temperature from 15 to 50°, doubling the reaction time from two to four hours, or using 100% water in place of 50% ethanol–water had little effect on the yield (50–60%) of monoalkylation product isolated. However, shortening the reaction time to 0.5 hr. or halving the ratio of resin to reactants reduced the yield (36–37%) slightly.

We have observed that the anion exchange resin, Amberlite IRA-400(OH$^-$), could rapidly exchange its labile hydroxyl ion with the enolate of the active methylene compound even in aqueous solution producing the resin (R$^-$) which was stable enough to isolate in the dry state (Table III). The resin (R$^-$) could subsequently react with alkyl halide (R'X) to give the resin (X$^-$) and the desired alkylation product. Treatment of the resin (R$^-$) with mineral acid (HX'), as expected, regenerated the starting active methylene compound and produced the resin (X'$^-$).

Experimental[14]

Materials.—The ethyl malonate and ethyl cyanoacetate were commercially available and redistilled before use. Cyanoacetamide, 2-alkyl-, 2-phenyl-, and 2-acetamidocyanoacetamides were prepared in the laboratory by known methods.[15-17] The anion exchange resin Amberlite IRA–400 was usually purchased as the chloride salt (16–60 mesh). The conversion of the resin to the hydroxyl form was accomplished by washing the resin with about 1 *N* sodium hydroxide until the eluate gave a negative silver nitrate test for chloride ion. The resin was then thoroughly washed with distilled water until the washings were neutral, dried in an oven for several hours at about 40°, and kept in a vacuum desiccator for 24 hr. before use.

Ethyl 2-Allyl- and 2,2-Diallylmalonate.—To a mixture of 3.2 g. (0.02 mole) of ethyl malonate, 8.8 g. (0.02 mole) of Amberlite IRA-400(OH$^-$) with a capacity of 2.3 meq./dry g. and 40 cc. of ethanol in a flask, there was added 2.42 g. (0.02 mole) of allyl bromide. After agitating for 2 hr. at room temperature, the resin was removed by filtration, washed with ethanol, the washings were combined with the original filtrate, and the entire mixture was gently distilled to remove the ethanol. The residual oil (3.95 g.) was analyzed by gas chromatography; column, silicone D.C. 550 3 m. × 6 mm.; 200°; He, 72 cc. per min. The internal standard indicated that three peaks appeared at retention times of 8.4, 16.2, and 30.5 min. were identical to those of ethyl malonate, ethyl 2-allylmalonate, and ethyl 2,2-diallylmalonate, respectively. The yields of ethyl 2-allyl- and 2,2-diallylmalonate were 2.42 g. (61%) and 0.60 g. (12%).

Ethyl 2-Ethyl- and 2,2-Diethylcyanoacetate.—Ethyl cyanoacetate (2.26 g., 0.02 mole), 8.8 g. (0.02 mole) of Amberlite IRA-400(OH$^-$), having a capacity of 2.3 meq./dry g., and 3.12 g. (0.02 mole) of ethyl iodide along with 45 cc. of ethanol were treated similarly as described in ethyl 2-allyl- and 2,2-diallylmalonate to give 2.7 g. of liquid product which was then analyzed by gas chromatography; column, silicone D.C. 550 3 m. × 6 mm.; 200°; He, 72 cc. per min. The internal standard indicated that three peaks appeared at retention times of 6.2, 8.6, and 12.6 min. were identical to ethyl cyanoacetate, ethyl 2-ethylcyanoacetate, and ethyl 2,2-diethylcyanoacetate, respectively. The yields of ethyl 2-ethyl- and 2,2-diethylcyanoacetate were 1.43 g. (51%) and 0.65 g. (19%).

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Table I

Alkylation of Ethyl Malonate and Ethyl Cyanoacetate with Alkyl Halides in the Presence of Amberlite IRA-400(OH^-)[a]

Compound	Alkyl halide	Product composition, %[b] Unalkylated	Monoalkylated	Dialkylated
$H_2C(CO_2C_2H_5)_2$	C_2H_5I	7	72	...
$H_2C(CO_2C_2H_5)_2$	C_3H_7I	11	55	...
$H_2C(CO_2C_2H_5)_2$	$CH_2{=}CH{-}CH_2Br$	14	61	12[c]
$H_2C(CN)CO_2C_2H_5$	C_2H_5I	12	51	19
$H_2C(CN)CO_2C_2H_5$	C_3H_7I	12	42	11
$H_2C(CN)CO_2C_2H_5$	$CH_2{=}CH{-}CH_2Br$	23	31	29[d]

[a] Molar equivalent each of the reactants and the resin along with ethanol were agitated at room temperature for two hours unless otherwise stated. [b] Analyzed by gas chromatography. See Experimental. Yields based on the active methylene compound used. [c] With two moles each of allyl bromide and the resin and one mole of ethyl malonate, the yield of dialkylation product was increased to 51% with a 46% of monoalkylation product. [d] With two moles each of allyl bromide and the resin and one mole of ethyl cyanoacetate, the dialkylation product was obtained exclusively; yield 97%.

Table II

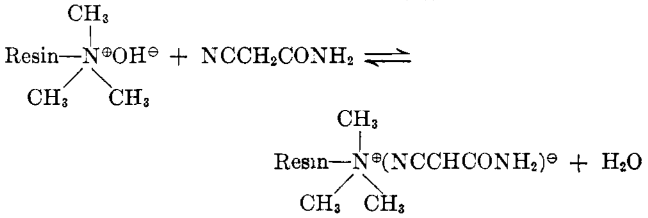
Alkylation of Cyanoacetamide and Its C-Substituted Derivatives with Alkyl Halides in the Presence of Amberlite IRA-400(OH^-)[a]

RCH(CN)CONH₂ R	R'X	Yield of monoalkylation product, %	M.p., °C.	Reported m.p., °C.
H	C_2H_5I	47	112–112.5	112.5–113.5[b]
H	C_3H_7I	34[c]	115–117.5	116–118[d]
H	$i\text{-}C_3H_7I$	17	127–128.5	124–125[d]
H	C_4H_9I	20[e]	122.5–124	125[f]
H	$CH_2{=}CH{-}CH_2Br$	28[g]	100–104	101–104[b]
C_2H_5	C_2H_5I	49	120.5–121.5	121[h]
C_2H_5	C_3H_7I	34	113–113.5[i]	116[j]
C_2H_5	$CH_2{=}CH{-}CH_2Br$	82	121.5–122.5[k,l]	
$i\text{-}C_3H_7$	C_2H_5I	48	110–111[k,m]	
$i\text{-}C_3H_7$	C_3H_7I	29	124.5–125[k,n]	
$i\text{-}C_3H_7$	$CH_2{=}CH{-}CH_2Br$	65	90–91[k,o]	
C_6H_5	C_2H_5I	63	116–117.5	117–117.5[b]
C_6H_5	C_3H_7I	35	115.5–116.5	115–116[b]
C_6H_5	$CH_2{=}CH{-}CH_2Br$	65	115–116	115–116[b]
CH_3CONH	C_2H_5I	50	205–206	205[b]
CH_3CONH	C_3H_7I	13	211–213.5	210–211[b]
CH_3CONH	$CH_2{=}CH{-}CH_2Br$	50	197–198	194–198[b]

[a] Molar equivalent each of the reactants and the resin along with ethanol–water (50 vol. %) were agitated at room temperature for two hours. [b] K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **26**, 4868 (1961). [c] Accompanied by a few per cent of 2, 2-dipropylcyanoacetamide, m.p. 152–153°; reported m.p. 153° (see *j*). [d] K. Shimo and R. Asami, *J. Chem. Soc. Japan* (*Pure Chem. Sect.*), **78**, 803 (1957). [e] Accompanied by a few per cent of 2,2-dibutylcyanoacetamide, m.p. 124–124.5°; reported m.p. 123° (see *f*). [f] J. C. Hessler and W. F. Henderson, *J. Am. Chem. Soc.*, **43**, 672 (1921). [g] Accompanied by 2,2-diallylcyanoacetamide, m.p. 129°; reported m.p. 128–129° (see *b*). The yield was 32% (based on allyl bromide). [h] Beilsteins "Handbuch Der Organischen Chemie," Vierte Auflage, Band II, p. 689. [i] *Anal.* Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.63; H, 8.77; N, 18.19. [j] M. Conrad and A. Zart, *Ann.*, **340**, 335 (1905). [k] New compound. [l] Recrystallized from ethanol–water (50 vol. %). *Anal.* Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.27; H, 7.73; N, 18.50. [m] Soluble in hot ligroin (b.p. 78–108°). *Anal.* Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.30; H, 9.04; N, 18.15. [n] Soluble in hot ligroin (b.p. 78–108°). *Anal.* Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.58; N, 16.65. Found: C, 64.20; H, 9.38; N, 16.62. [o] Soluble in hot ligroin (b.p. 78–108°). *Anal.* Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.03; H, 8.10; N, 17.06.

Table III

Anion Exchange Reaction of Amberlite IRA-400(OH^-) with Cyanoacetamide in Water[a]



$$\mathrm{Resin{-}\overset{CH_3}{\underset{CH_3\quad CH_3}{N^{\oplus}}}OH^{\ominus} + NCCH_2CONH_2 \rightleftharpoons Resin{-}\overset{CH_3}{\underset{CH_3\quad CH_3}{N^{\oplus}}}(NCCHCONH_2)^{\ominus} + H_2O}$$

Starting $NCCH_2CONH_2$, mole	Exchanged $NCCH_2CONH_2$,[b] mole
0.01	0.0074
.02	.0098
.03	.0110
.05	.0129

[a] A 0.02-mole sample of the resin along with 20 cc. of water was used. The reaction was operated at 20° with mechanical agitating for ten minutes. [b] Bonded to the nitrogen atom of the resin in the form of enolate anion; calculated from the recovery of the cyanoacetamide unconverted; by treating with alkyl halide gave the corresponding C-alkylation product; while, with mineral acid, regenerated the cyanoacetamide; see Experimental.

2-Propylcyanoacetamide.—Propyl iodide (3.4 g., 0.02 mole) was added to a mixture of 1.68 g. (0.02 mole) of cyanoacetamide in 30 cc. of ethanol–water (50 vol. %) and 7.5 g. (0.02 mole) of Amberlite IRA-400(OH^-) with a capacity of 2.7 meq./dry g., then agitated for 2 hr. at room temperature. At the end of the reaction period, the resin was filtered off and washed on the filter with ethanol–water. The filtrate was evaporated to dryness under reduced pressure, and the remaining solids were recrystallized from water to give 0.85 g. (34%) of 2-propylcyanoacetamide along with 0.05 g. (3%) of 2,2-dipropyl derivative, sparing soluble in hot water.

2-Isopropyl-2-ethylcyanoacetamide.—To a mixture of 1.26 g. (0.01 mole) of 2-isopropylcyanoacetamide in 25 cc. of ethanol-water (50 vol. %) and 3.7 g. (0.01 mole) of Amberlite IRA-400(OH^-) with a capacity of 2.7 meq./dry g., there was added 1.6 g. (0.01 mole) of ethyl iodide. After agitating for 2 hr. at room temperature, the resin was removed by filtration, and washed with ethanol–water. The filtrate was evaporated to dryness under reduced pressure, and the remaining solids were dissolved in 25 cc. of hot ligroin (b.p. 78–108°). Insoluble 2-isopropylcyanoacetamide (0.3 g., 24%) was recovered, the desired product was obtained thereafter from the solution on cooling. The yield was 0.74 g. (48%).

Anion Exchange Reaction of Amberlite IRA-400(OH^-) with Cyanoacetamide in Water.—Cyanoacetamide (1.68 g., 0.02 mole) in 20 cc. of water was mixed with 7.3 g. (0.02 mole) of Amberlite IRA-400(OH$^-$) having a capacity of 2.8 meq./dry g. and agitated for 10 min. at 20°. Then the resin was filtered off and washed thoroughly with water on the filter. The filtrate was evaporated to dryness under reduced pressure to recover unconverted 0.88 g. (52%) of cyanoacetamide. Thus, 0.82 g. of cyanoacetamide had exchanged with the hydroxyl ion of the resin during the course of the reaction. The entire washed resin was treated with 2.4 g. (0.02 mole) of allyl bromide in 20 cc. of ethanol for 0.5 hr. at room temperature under shaking. The corresponding 2,2-diallylcyanoacetamide (0.58 g.) was thereby obtained. On the other hand, when treated with 1.66 cc. (0.02 mole) of concentrated hydrochloric acid in ethanol for 10 min., the resin regenerated 0.45 g. of cyanoacetamide unchanged.

Acknowledgment.—The authors wish to express their appreciation to Mr. T. Sakan and to Mr. S. Matsuura for their able technical assistance. They are also indebted to the Tokyo Organic Chemical Industries Ltd., for supplying Amberlite IRA-400 throughout this work.

Studies on Resin Acids. 1-Ketonordehydroabietane

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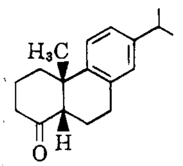
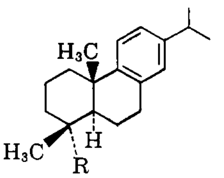
The preparation of 1-ketonordehydroabietane (I) from dehydroabietic acid has been reinvestigated. When the original preparation was repeated it was found that the olefinic precursor of I was contaminated with the tertiary alcohol (IIc), and a modified approach *via* the Cope reaction was employed. Oxidation of III with permanganate–manganese sulfate–pyridine gave 1-α-carboxy-9-ketonordehydroabietane (IV), which was also synthesized by an alternate route. Ozonization of the olefin from the Cope reaction gave I in good yield. I was shown to have a *cis* A-B ring fusion, based on its optical rotatory dispersion curve.

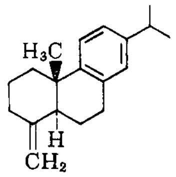
The preparation of 1-ketonordehydroabietane (I) either from dehydroabietic acid[2,3] or by total synthesis[4] has received considerable attention in the past few years. The need for rather large quantities of I has led us to reinvestigate in detail the preparation of this compound. Of the several methods reported for obtaining this material the most attractive, in spite of rather poor yields, appeared to be that of Zeiss and Martin.[2] Conversion of dehydroabietic acid (IIa) to the secondary amine (IIb) proceeded as reported; however, the Hofmann elimination product, reported to be the olefin (III), showed distinct hydroxyl absorption in the infrared, and on chromatography could be separated into a mixture of the olefin (40%) and a substance having the properties expected of the tertiary alcohol (IIc, 31%). The modification of the Hofmann reaction employed, using potassium carbonate and methyl iodide,[2] is one which would not be expected to afford high yields of olefin,[5] and the formation of alcohols in the Hofmann reaction is not without precedent.[5] When the secondary amine was converted to the corresponding tertiary amine (IId), and the quaternary hydroxide pyrolyzed,[2] the product still showed distinct hydroxyl absorption in the infrared, and this method was not investigated in any greater detail. Good yields of pure exocyclic olefin were ultimately obtained by converting the tertiary amine to the N-oxide (IIe) with peracetic acid,[6] followed by pyrolysis. Direct thermal treatment of the N-oxide gave much charring, and consequently the N-oxide was boiled in dimethylformamide, whereupon the olefin was smoothly produced in good yield. The choice of dimethylformamide as a solvent was based on the observation of Cram, *et al.*,[7] that the rate of many elimination reactions are enhanced by the use of the very polar solvent, dimethyl sulfoxide. It was felt that a similar polar solvent, dimethylformamide, would also show this rate-enhancing effect, and would provide a suitable alternative to direct pyrolysis. Although the possibility of contamination of the exocyclic olefin formed in this manner with double bond isomers cannot be *a priori* excluded, the definitive experiments of Cope on monocyclic systems,[8] combined with the conversion of the olefin thus formed to a crystalline diol in high yield (*vide infra*) makes this possibility seem most unlikely.



I



IIa. R = CO_2H
b. R = $NHCH_3$
c. R = OH
d. R = $N(CH_3)_2$
e. R = $\overset{\displaystyle O}{\overset{|}{N}}(CH_3)_2$



III

When an attempt was made to oxidize the olefin, prepared by the Hofmann elimination, to the desired ketone (I), using permanganate–manganese sulfate–pyridine,[9] a complex mixture of products was obtained, which could be separated into acid and neutral fractions. The multicomponent neutral fraction was devoid of the desired ketone and was not investigated further. The acid fraction showed carbonyl absorption in the infrared at 5.85 and 5.97 μ, indicating that the material was a keto acid, with a conjugated ketonic carbonyl.

Analysis of the dinitrophenylhydrazone of the ethyl ester of this keto acid indicated that the parent compound had the empirical formula, $C_{19}H_{24}O_3$. This

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