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Specific Solvent Effects in the Alkylation of Enolate Anions. III. Preparative Alkylations in Dimethylformamide

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Received June 27, 1960

To help define the utility of dimethylformamide as a reaction medium for the alkylation of enolate anions, results obtained under a variety of conditions are reported for the alkylation of alkali and alkaline earth metal salts of acetoacetic ester and of some of its monosubstituted derivatives. In addition, similar reactions of alkali metal derivatives of nine other active methylene compounds are described. Whenever possible, comparisons are made with identical or similar reactions carried out in other solvent systems. Both the advantages and the limitations of dimethylformamide as a solvent are pointed out. Also reported are qualitative tests of the efficacy of the sodium hydride–dimethylformamide system for the conversion of twenty-five active methylene compounds to corresponding sodium derivatives. The preparation and isolation of the anhydrous sodium and potassium enolates of acetoacetic ester are described using sodium and potassium hydroxides as bases. Some hitherto unrecorded properties of these salts are described.

During the decade since Sheehan and Bolhofer[1] first recommended the use of dimethylformamide (DMF) as a solvent in the alkylation of potassium phthalimide, this liquid has enjoyed wide application as the solvent of choice in many alkylation reactions.[2] Although a number of isolated examples have appeared[3] in which dimethylformamide, usually in combination with benzene or ethanol, has been employed as solvent in the carbon-alkylation of enolate anions, only the brief report of Marshall and Cannon[4] approaches anything resembling a systematic investigation in this area of the effect of dimethylformamide on products and yields. They found that the presence of dimethylformamide, again in combination with benzene, notably increased the yields of a few alkylations of sodium enolates of monosubstituted acetoacetic esters.

Quantitative observation[5a] of the considerable accelerating effect of dimethylformamide on the rate of alkylation of sodio-malonates in benzene solution, and the development of a reasonable explanation of this action,[5b] has led to the routine use of this solvent (usually in undiluted form[6]) in our laboratories. This paper reports many of the alkylations of enolate salts which have been carried out during the past seven years. Whenever possible, comparisons are made with the same or similar reactions conducted here or elsewhere under more conventional solvent conditions. It is hoped that others will thereby gain a more serviceable understanding of the scope and limitations of the utility of dimethylformamide in this important area of organic synthesis.

Results are summarized in three tables. Several tentative conclusions are derivable from Table I. Unless time is a critical factor, dimethylformamide offers little advantage over ethanol[7-9] as a solvent in the alkylation of unsubstituted sodio-acetoacetic ester with primary alkyl bromides. Optimum yields usually varied from 60 to 70% in either solvent. The main factor preventing higher yields in dimethylformamide (as in other solvents) appeared to be the tendency to form dialkylated acetoacetic esters. Higher boiling residues were obtained in all the runs of Table I. When primary aliphatic chlorides were used instead of the bromides, dimethylformamide exhibited clear superiority over ethanol.[8] With some exceptions (*cf. i*-butyl chloride) yields only 10 to 15% lower than those for the corresponding bromides could be expected.

Although isopropyl bromide behaved in these reactions much like a primary bromide, *t*-butyl bromide, as in conventional alkylations,[10] was

(1) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, 72, 2786 (1950).

(2) For a review through 1957 see, *DMF, a Review of Catalytic Effects and Synthetic Applications*, Grasselli Chemicals Department, E. I. du Pont de Nemours and Co., Wilmington, Del.

(3) (a) G. Stork and A. Burgstahler, *J. Am. Chem. Soc.*, 73, 3544 (1951); (b) K. Dittmer, J. Shapira, and R. Shapira, *ibid.*, 75, 3655 (1953); (c) F. Ramirez and A. P. Paul, *J. Org. Chem.*, 19, 183 (1954); (d) H. R. Snyder and P. L. Cook, *J. Am. Chem. Soc.*, 78, 969 (1956); (e) H. Conroy and R. A. Firestone, *J. Am. Chem. Soc.*, 78, 2290 (1956); (f) E. L. Eliel, P. H. Wilken, and F. T. Fang, *J. Org. Chem.*, 22, 231 (1957); (g) N. A. Nelson and R. B. Garland, *J. Am. Chem. Soc.*, 79, 6313 (1957); (h) A. L. Searles and D. Ressler, *J. Am. Chem. Soc.*, 80, 3656 (1958); (i) E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, 80, 4659 (1958); (j) D. P. Tschudy and A. Collins, *J. Org. Chem.*, 24, 556 (1959).

(4) F. J. Marshall and W. N. Cannon, *J. Org. Chem.*, 21, 245 (1956).

(5) (a) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, 82, 2895 (1960). (b) H. E. Zaugg, *J. Am. Chem. Soc.*, 82, 2903 (1960).

(6) The rate of alkylation in pure dimethylformamide of sodio-*n*-butylmalonic ester with *n*-butyl bromide is roughly 1000 times that in pure benzene—H. E. Zaugg, unpublished.

(7) C. S. Marvel and F. D. Hager, *Org. Syntheses*, Coll. Vol. I, 248 (1941).

(8) W. B. Renfrow and A. Renfrow, *J. Am. Chem. Soc.*, 68, 1801 (1946).

(9) C. A. Bischoff, *Ber.*, 28, 2616 (1895).

(10) A. C. Cope, H. L. Holmes, and H. O. House in *Org. Reactions*, 9, 139 (1957).

TABLE I

ALKYLATION OF SODIO-ACETOACETIC ESTERS IN DIMETHYLFORMAMIDE

$$[CH_3COC(R)COOC_2H_5]Na \xrightarrow[DMF]{R'X} CH_3COC(R)(R')COOC_2H_5 + NaX$$

R	R'X	Time, Hr.	Temp.	Yield, %[a]	B.P.	Mm.	n_D^{25}
H	CH_3I	3	95–100	23	181–184	atm.	1.4179
H	C_2H_5Br	5	80–120	74[b]	85–90	18–20	1.4214
H	n-C_3H_7Br	3	95–100	57[c]	82–85	8–9	1.4273
H	n-C_3H_7Cl	16	75–120	45	82–85	8–9	1.430
H	i-C_3H_7Br	2	95–100	62[d]	83–86	9–10	1.4280
H	i-C_3H_7Cl	48	85–100	0			
H	n-C_4H_9Br	3	95–100	60	93–96	8	1.4298[e]
H	n-C_4H_9Cl	20	90–95	47	92–96	8	1.4318[e]
H	i-C_4H_9Br	16	80–100	56	85–97	8	1.4270
H	i-C_4H_9Cl	20	80–100	0			
H	t-C_4H_9Br	2	75	0[f]			
H	n-$C_5H_{11}Br$	2	95–100	70	101–105	8	1.4328[g]
H	n-$C_5H_{11}Cl$	20	80–100	52	102–107	8–9	1.4345[g]
H	$C_2H_7CH(CH_3)Br$	7	140–150	19[h]	117–120	20	1.4321
C_2H_5	C_2H_5Br	3	70–100	46	92–98	14	1.4291
C_2H_5	n-C_3H_7Br	3	80–100	63	116–118	20	1.4322
C_2H_5	i-C_3H_7Br	3	80–100	56	114–116	20	1.4396
C_2H_5	n-C_4H_9Br	18	140–150	50	84–86	0.8	1.4370
C_2H_5	n-$C_5H_{11}Br$	3	80–100	55	130–134	5	
C_2H_5	$C_6H_5CH_2Cl$	3	80–100	63	135–138	2.5	1.5008
n-C_3H_7	CH_3I	10	80–120	47[i]	104–108	20	1.4260
n-C_3H_7	C_2H_5Br	10	80–130	65	112–116	20	1.4297
n-C_4H_9	CH_3I	10	80–120	53	119–122	20	1.4305

[a] Preparations of most of these esters have been reported.[4,9,14,15] When the present work was carried out, gas chromatographic analysis was not available. Identity and purity of products were checked periodically by elemental analyses. [b] Reaction in diethyl carbonate (100° for 3 days) gave 29% of product, b.p. 82–83° (14 mm.), n_D^{25} 1.4216. [c] P. Ceuterick, *Bull. soc. chim. Belg.*, **45**, 545 (1936); *Chem. Abstr.*, **31**, 919 (1937), reported b.p. 90° (10 mm.) and n_D 1.4271. Reaction in benzene (reflux for 112 hr.) gave 14% of product, b.p. 100–105° (16–18 mm.). Reaction in diethyl carbonate (100° for 3 days) gave 46% of product, b.p. 100–104° (14 mm.), n_D^{25} 1.4246. [d] Inverse addition of the sodioacetoacetic ester in dimethylformamide to a stirred dimethylformamide solution of the isopropyl bromide held at 65 to 85° gave a 63% yield of product, b.p. 98–102° (26 mm.). When sodio-acetoacetic ester, prepared from sodium ethoxide in ethanol, was alkylated with isopropylbromide in the usual way in dimethylformamide (after removal of all ethanol), a 60% yield of product, b.p. 97–101° (23 mm.), n_D^{25} 1.4280 was obtained. [e] P. Ceuterick[c] reported b.p. 104° (12 mm.) and n_D 1.4301. [f] Copious evolution of isobutylene was noted during the reaction. [g] P. Ceuterick[c] reported b.p. 117° (10 mm.) and n_D 1.4326. [h] *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.78; H, 10.00. [i] This reaction failed completely in diethyl carbonate.

seriously dehydrohalogenated. Furthermore, in view of Nace's[11] observations concerning the facile elimination in dimethylformamide of sulfonate esters of secondary alcohols, these substances as well as the corresponding secondary iodides[12] should not be used as alkylating agents in this solvent.

As observed previously,[4] dimethylformamide appears to offer definite advantages as a reaction medium for the alkylation of enolates of monosubstituted acetoacetic esters. Yields[13] (Table I) compare favorably with those attainable in the alkylation of ethyl acetoacetate itself and exceed corresponding yields obtainable[8] in ethanol. Only the use of potassium t-alkoxides in t-alcohols[8,14] seems to give better yields.

Several of the alkylations of Table I were also performed in diethyl carbonate, a solvent of considerable utility for reactions of this type.[15] The superiority of dimethylformamide with regard to both yield and reaction time was clearly evident (Table I, footnotes b, c, i).

Table II summarizes information gained by alkylating (mostly with n-butyl bromide) different salts of acetoacetic ester. Of interest is the utilization of salts prepared from sodium and potassium hydroxides. Although these bases previously have been employed[16] with success in acetoacetic ester alkylations, removal of water of neutralization prior to treatment with alkylating agent

(11) H. R. Nace, *J. Am. Chem. Soc.*, **81**, 5428 (1959).

(12) Even primary iodides are not recommended as alkylating agents in dimethylformamide because sodium iodide, formed in the course of the reaction, complexes with the solvent. An iodide alkylation in dimethylformamide usually sets to a non-stirrable semi-solid mass during the course of the reaction. Incidentally, this does not occur when dimethylacetamide is used in place of dimethylformamide.

(13) As an extreme test, an attempt was made to alkylate the sodium salt of i-propyl acetoacetic ester with i-propyl bromide in dimethylformamide. Although the reaction went to neutrality (elimination) no pure dialkylated product could be isolated. To the authors' knowledge, di-i-propyl acetoacetic ester remains unknown.

(14) W. B. Renfrow, *J. Am. Chem. Soc.*, **66**, 144 (1944).

(15) V. H. Wallingford, M. A. Thorpe, and A. H. Homeyer, *J. Am. Chem. Soc.*, **64**, 580 (1942).

(16) (a) A. Brändström, *Acta Chem. Scand.*, **13**, 607 (1959) (b) A. T. Babayan, N. Gambaryan, and N. P. Gambaryan, *Zhur. Obshchei Khim.*, **24**, 1887 (1954); *Chem. Abstr.*, **49**, 10879 (1955).

TABLE II

ALKYLATION OF SALTS OF ACETOACETIC ESTER

$$[CH_3COCHCOOC_2H_5]_nM^{n+} \xrightarrow[\text{Solvent}]{RX} CH_3COCH(R)COOC_2H_5 + MX_n$$

M[a]	RX	Solvent	Time, hr.	Temp.	Yield, %	B.P.	Mm.	n_D^{25}
Na	n-C_4H_9Br	DMF	3	95–100	60[b]	93–96	8	1.4298
Na	n-C_4H_9Br	20% $(C_2H_5)_3N$ in C_6H_6	24	82–84	59	102–108	13	1.4280
Na	n-C_4H_9Br	10% DMF in C_6H_6[l]	14[c]	83–85	72	94–99	9	1.4290
K	n-C_4H_9Br	C_6H_6	93	79–81	65	92–95	8	1.4270
K	n-C_4H_9Br	C_2H_5OH[m]	5.5[d]	80–82	55	97–102	11	1.4296
K	n-C_4H_9Br	20% $(C_2H_5)_3N$ in C_6H_6	24	82–84	74	103–109	14	1.4298
K	n-C_4H_9Br	10% DMF in C_6H_6[l]	14[e]	83–85	71	92–97	8	1.4297
K	n-C_4H_9Cl	DMF[m]	24[f]	95–100	61[g]	98–105	12	1.4310
K	n-C_4H_9Br	DMF	2	95–100	72	94–100	10	1.4310
K	n-C_4H_9Br	DMF	5	95–100	59[h]	95–98	9	1.4340
K	n-C_4H_9Br	DMF	[i]		64	97–100	11	1.4330
K	n-C_4H_9Br	DMF	70	20–25	64[j]	93–97	9	1.4315
K	n-C_4H_9Br	DMF[m]	43[k]	3–5	65	98–102	12	1.4319
Mg[n]	n-C_4H_9Br	DMF	8	95–100	24	107–110	18	1.4295
Mg	n-C_4H_9Br	DMF	3	130–142	28[o]	106–112	18	1.4304
Mg	$C_6H_5CH_2Cl$	DMF	6	95–100	42[p]	162–168	19	1.4988
Ca[n]	n-C_4H_9Br	DMF	10	95–100	58	110–115	18	1.4285
Ca	n-C_4H_9Br	DMF	2	130–150	45[q]	115–121	23	1.4297
Ca	n-C_4H_9Br	DMF	0.6	130–150	54	116–122	23	1.4290
Ca	n-C_4H_9Br	DMF	24	75–80	60	113–116	21	1.4285
Ca	n-C_4H_9Br	DMF	7	95–100	60	107–110	16	1.4288
Ca	$C_6H_5CH_2Cl$	DMF	6	75–80	50[r]	164–170	19	1.4999
Ba[s]	n-C_4H_9Br	DMF in C_6H_6[t]	48	80–85	22[q]	101–105	15	1.4298
Ba	n-C_4H_9Br	DMF[u]	26	55–70	42	105–1[illegible]	17	1.4295
Ba	n-C_4H_9Br	DMF[v]	4	95–100	56	105–109	18	1.4302
Ba	n-C_4H_9Br	DMF[u]	4	95–100	53	102–108	18	1.4294
Ba	n-C_4H_9Br	DMF[w]	6	95–100	53	110–114	20	1.4305
Ba	n-C_4H_9Br	DMF[u]	3	130–150	41	108–111	19	1.4314
Cu[z]	n-C_4H_9Br	DMF	7	95–100	0			

[a] See experimental for preparation of salts. With the exception of the first entry (taken from Table I) all sodium and potassium salts were prepared from sodium hydroxide and potassium hydroxide respectively. [b] Analytically pure. [c] Reaction half-time was 240 min. It did not go to neutrality, but showed good second-order kinetics (straight line plot of 1/c *vs.* t) over the first 60% of reaction. [d] Reaction half-time was 20 min. Second-order kinetics over 92% of the reaction. [e] Reaction half-time was 88 min. Second-order kinetics over 80% of the reaction which went to 84% completion (by titration) in 14 hr. [f] Reaction half-time was 100 min. Second-order kinetics over 66% of the reaction 85% complete in 24 hr. [g] A small quantity of dehydroacetic acid was isolated from high-boiling fractions. [h] Also isolated was a 5% yield of di-n-butylacetoacetic ester, b.p. 125–126° (9 mm.), n_D^{25} 1.4388. *Anal.* Calcd. for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81; O, 19.81. Found: C, 69.08; H, 10.78; O, 20.07. [i] Conditions: 16 hr. at room temperature, 1 hr. at 60°, 3 hr. at 75°, and 2 hr. at 95–100°. [j] Also isolated a 5% yield of di-n-butylacetoacetic ester, b.p. 127–130° (13 mm.), n_D^{25} 1.4398. [k] Reaction half-time was 1200 min. Second-order kinetics over 70% of the reaction 87% complete in 43 hr. [l] One liter of solvent for a one mole run. [m] 200 ml. of solvent for a one mole run. [n] In all reactions of magnesium and calcium salts, 150 ml. of dimethylformamide and 0.44 mole of alkylating agent were used with 0.20 mole of the salt. [o] Large quantities of butene were evolved during this reaction. Also isolated was a small quantity of 2-heptanone, b.p. 146–147° (atm.), n_D^{25} 1.4065. *Anal.* Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.51; H, 12.58; infrared-spectrum identical with that of an authentic speciman. [p] Also isolated was a 9% yield of dibenzylacetoacetic ester, b.p. 168–172° (0.6 mm.), n_D^{25} 1.5430, m.p. 49–55°. [q] Also isolated was a small quantity of 2-heptanone (*cf.* footnote o). [r] Also isolated was an 11% yield of dibenzylacetoacetic ester (*cf.* footnote p). [s] 0.2 mole of the salt and 0.5 mole of n-butyl bromide were used in all reactions of the barium derivative. [t] 30 ml. of dimethylformamide in 400 ml. of benzene No noticeable reaction occurred in benzene alone. [u] 150 ml. [v] 250 ml. [w] 300 ml. [z] 0.4 mole of the copper derivative, m.p. 188–193°, in 500 ml. of dimethylformamide and 1.0 mole of n-butyl bromide.

has not been a characteristic precaution. It has now been found that essentially anhydrous salts[17] are obtainable by azeotropic removal of the water of neutralization by means of refluxing benzene. No detectable hydrolysis of the ester occurred with either hydroxide. Yields of alkylated products obtained from the sodium salt prepared in this way were quite comparable to those derived from enolate prepared from sodium hydride under completely anhydrous conditions (Table I).

(17) Our anhydrous sodio-acetoacetic ester melted at 180° and had a correct analysis. Sidgwick and Brewer[18] reported a m.p. 108° for this substance. However, an interesting characteristic of the anhydrous salt is that, on a humid day it takes up atmospheric moisture to form a hemihydrate, m.p. 117–121°, in less time than is required to get it into a melting point capillary. This accounts for the low melting point reported by the British workers.

The potassium salt very likely behaves similarly. Our melting point (150°) is considerably higher than that (106°) previously reported.[18] The anhydrous sodium salt, unlike the potassium salt, can be stored in a tightly stoppered bottle for years with little sign of deterioration (darkening or lowered melting point).

(18) N. V. Sidgwick and F. M. Brewer, *J. Chem. Soc.*, 2379 (1925).

Although the potassium enolate alkylated more rapidly (Table II, footnotes c and e) than the sodium derivative, yields were essentially the same for both. This is what the Renfrows[8] observed with ethanol as solvent.

The effect of solvent is more strikingly demonstrated in the alkylation of the calcium derivative of acetoacetic ester. Hackman[19] obtained a 42% yield of monoethylated product using ethyl iodide in ethanol (seven hours reflux). In contrast, optimum conditions in dimethylformamide gave a 60% yield of product with less reactive *n*-butyl bromide. This performance could not be improved in going to the barium salt; and the magnesium enolate gave decidedly inferior yields.

Although the copper derivative of acetoacetic ester gives good yields of C-acyl derivatives with certain acid chlorides in chloroform solution,[20] attempted alkylation with *n*-butyl bromide in dimethylformamide failed completely.

Other results from Table II deserving passing mention are the fair yield (61%) obtained from the potassium enolate with *n*-butyl chloride, and the 65% yield attained with *n*-butyl bromide at low reaction temperature (3–5°). However, these successes with the potassium enolate in dimethylformamide lose some of their luster when it is noted that, given time (ninety-three hours), reaction with *n*-butyl bromide proceeds just as well (65%) in refluxing benzene. In this respect the potassium salt differs from the sodium salt (see Table I, footnote c).

In addition to the usual side reaction leading to dialkylation (especially marked with benzyl chloride), appreciable ketonic cleavage to 2-heptanone occurred in most of the *n*-butyl bromide runs. This ketone was isolated in pure form in several instances. Also, from some of the runs requiring long reaction times at elevated temperatures, small amounts of dehydroacetic acid were obtained.

Table III lists the results of miscellaneous alkylations (and two acylations) carried out in connection with other synthetic work. Although enolates of malonic ester, unlike acetoacetic ester, can generally be alkylated in good yields under a variety of conditions,[21] the first two entries are included to show the striking increase in reactivity of the potassium enolate[22] in going from a benzene to a dimethylformamide environment. The highly exothermic nature (Table III, footnote *b*) of the dimethylformamide reaction is worthy of note.

The difference in outcome of the two reactions (one in ethanol and one in dimethylformamide) of benzhydryl bromide with sodiomalonic ester, illustrates the relative superiority of dimethylformamide in reactions involving readily solvolyzed halides.[23]

The four reactions involving sodium derivatives of 3-phenyl-2-benzofuranone and 3-phenylphthalide exemplify situations in which total failure in benzene or toluene solution becomes moderate success in dimethylformamide.[24]

It is interesting to compare the result of the benzylation of diphenylacetic acid using two moles of sodium hydride in dimethylformamide with that of Hauser and Chambers[25] who employed two moles of potassium amide in liquid ammonia. Under their conditions, the dipotassium salt formed first and then benzylated preferentially at the α-carbon to give only the trisubstituted *acid*. That only benzyl *esters*, both α-benzylated (45%) and unsubstituted (26%) were obtained with sodium hydride in dimethylformamide indicates that, under these conditions, the disodium salt was not formed first. Esterification to benzyl diphenylacetate must have preceded α-hydrogen displacement which was then followed by α-benzylation.

Smooth α-alkylation of preformed ethyl diphenylacetate is exemplified by both methylation and benzylation in good yields (87% and 78%) using sodium hydride in dimethylformamide. This represents some improvement over conditions most often used in the past.[26] Extension to the alkylation of esters of the analogous fluorene- and xanthene-9-carboxylic acids likewise appears promising (Table III). The one failure encountered in this group of monoesters, namely, attempted alkylation with ethyl (β-chloroethyl) sulfide, is not surprising in view of the existing recognition[27] of the unusual ease with which compounds of this type undergo dehydrohalogenation.

Two examples (one barely successful) of the acylation of the sodium derivative of ethyl diphenylacetate are included in Table III to show that, even though acid chlorides are known[28] to react with dimethylformamide to give *N,N*-dimethylamides, C-acylation of enolate anions in dimethylformamide can be competitive.

One more side reaction which may occur with certain enolates in dimethylformamide remains to be mentioned. When the sodium derivative of phenylacetonitrile was allowed to stand in dimethylformamide at room temperature for five

(19) R. H. Hackman, *J. Chem. Soc.*, 2505 (1951).
(20) W. J. Barry, *J. Chem. Soc.*, 670 (1960).
(21) Reference 10, pp. 132, 164.
(22) Likewise obtained from potassium hydroxide.
(23) Compare reference 10, p. 124.
(24) It should be noted that C. R. Hauser, M. T. Tetenbaum, and D. S. Hoffenberg, *J. Org. Chem.*, **23**, 861 (1958), reported 77% and 100% yields, respectively, in the alkylation of 3-phenylphthalide with the highly reactive benzyl and benhydryl chlorides. They used sodium and potassium amides in liquid ammonia.
(25) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).
(26) Compare reference 10, pp. 135 and 285.
(27) K. Gundermann *Chem. Ber.*, **88**, 1432 (1955); K. Gundermann and R. Thomas, *Chem. Ber.*, **89**, 1263 (1956).
(28) G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954).

TABLE III

ALKYLATION OF SALTS OF ACTIVE METHYLENE COMPOUNDS

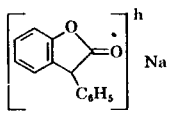
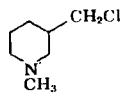
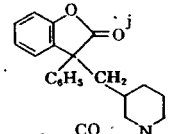
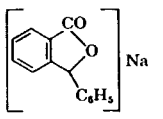
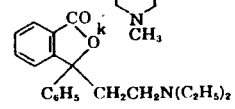
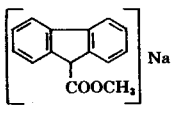
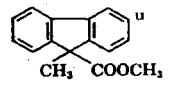
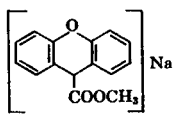
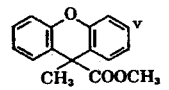
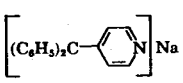
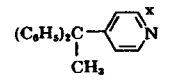
Salt	Salt Former	Solvent	Alkylating Agent	Time, Hr.	Temp.	Product	Yield, %
$[CH(COOC_2H_5)_2]K$	KOH	C_6H_6	n-C_4H_9Br	66	80	n-$C_4H_9CH(COOC_2H_5)_2$[a]	22
$[CH(COOC_2H_5)_2]K$	KOH	DMF	n-C_4H_9Br	0.5	100[b]	n-$C_4H_9CH(COOC_2H_5)_2$[c]	95
$[CH(COOC_2H_5)_2]Na$	$NaOC_2H_5$	C_2H_5OH	$(C_6H_5)_2CHBr$	4	78	$(C_6H_5)_2CHCH(COOC_2H_5)_2$[d]	24
						+ $(C_6H_5)_2CHOC_2H_5$[e]	51
$[CH(COOC_2H_5)_2]Na$	NaH	DMF	$(C_6H_5)_2CHBr$	2	50–100	$(C_6H_5)_2CHCH(COOC_2H_5)_2$[f]	59
$[(C_6H_5)_2CHC(COOC_2H_5)_2]Na$	NaH	DMF	C_2H_5Br	4	80–100	$(C_6H_5)_2CHC(COOC_2H_5)_2$[g]	75
						C_2H_5	
	NaH	C_6H_6		20	80		0
	NaH	50% DMF–C_6H_6		16	80–90		20
	$NaNH_2$	$C_6H_5CH_3$	$(C_2H_5)_2NCH_2CH_2Cl$	16	40–50		0
	NaH	DMF	$(C_2H_5)_2NCH_2CH_2Cl$	20	25–30		32
$(C_6H_5)_2CHCOONa$	NaH	DMF	$C_6H_5CH_2Cl$[l]	7	80–85	$(C_6H_5)_2C(CH_2C_6H_5)COOCH_2C_6H_5$[m]	45
						+ $(C_6H_5)_2CHCOOCH_2C_6H_5$[n]	26
$[(C_6H_5)_2CCOOC_2H_5]Na$	NaH	DMF	$(CH_3)_2SO_4$	18	95–100	$(C_6H_5)_2C(CH_3)COOC_2H_5$[o]	87
$[(C_6H_5)_2CCOOC_2H_5]Na$	NaH	DMF	$C_6H_5CH_2Cl$	7	30–50	$(C_6H_5)_2C(CH_2C_6H_5)COOC_2H_5$[p]	78
$[(C_6H_5)_2CCOOC_2H_5]Na$	NaH	DMF	$C_2H_5SCH_2CH_2Cl$	16	25–35		0[q]
$[(C_6H_5)_2CCOOC_2H_5]Na$	NaH	DMF	C_6H_5COCl[r]	20	25–35	$(C_6H_5)_2C(COC_6H_5)COOC_2H_5$[s]	41
$[(C_6H_5)_2CCOOC_2H_5]Na$	NaH	DMF	$C_6H_5OCH_2COCl$[r]	20	25–35	$(C_6H_5)_2C(COCH_2OC_6H_5)COOC_2H_5$[t]	6
	NaH	DMF	$(CH_3)_2SO_4$	18	95–100		96
	NaH	DMF	$(CH_3)_2SO_4$	18	95–100		84[w]
	$NaNH_2$	C_6H_6	CH_3I	2	80		23
	NaH	DMF	$(CH_3)_2SO_4$	20	25		53

TABLE III (*Continued*)

[a] B.p. 100–105° (8 mm.), n_D^{25} 1.4212. P. A. Levene and F. A. Taylor *J. Biol. Chem.*, 54, 358 (1922) reported a 75% yield (sodium salt in ethanol with *n*-butyl iodide), b.p. 122° (12 mm.), n_D^{20} 1.4222. R. Adams and C. S. Marvel, *J. Am. Chem. Soc.*, 42, 310 (1920) reported a 90% yield (sodium salt in ethanol with *n*-butyl bromide), b.p. 235–240°. [b] Temperature of the reaction rose spontaneously from 35° to 100° in less than 3 min. [c] B.p. 105–108 (10 mm.), n_D^{25} 1.4212. [d] B.p. 150–157° (0.1 mm.), n_D^{25} 1.5350. [e] B.p. 144° (10 mm.), n_D^{25} 1.5520. [f] B.p. 156–160° (0.2 mm.), n_D^{25} 1.5344. N. Campbell and H. Wang, *J. Chem. Soc.*, 2186 (1949) reported preparation of this compound in 49% yield using the sodium salt in ethanol with benzhydryl bromide. [g] B.p. 164–167° (0.1 mm.), n_D^{25} 1.5350, m.p. 67–69° (from hexane). *Anal.* Calcd. for $C_{23}H_{20}O_4$: C, 74.55; H, 7.39; O, 18.06. Found: C, 74.73; H, 7.43; O, 18.18. Campbell and Wang[f] allylated diethyl benzhydrylmalonate (sodium salt in ethanol with allyl bromide) in only 39% yield. [h] A, Löwenbein and H. Simonis, *Ber.*, 57, 2040 (1924). [i] R. F. Feldkamp, J. A. Faust, and A. J. Cushman, *J. Am. Chem. Soc.*, 74, 3831 (1952). [j] B.p. 175–176° (0.5 mm.), n_D^{25} 1.5747. *Anal.* Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.65; H, 7.67. Hydrochloride, m.p. 235–236° (from *i*-propyl alcohol). *Anal.* Calcd. for $C_{21}H_{24}ClNO_2$: C, 70.48; H, 6.76. Found: C, 70.53; H, 6.91. [k] Isolated as the hydrochloride, m.p. 183–184° (from ethanol). *Anal.* Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.46; H, 6.99; N, 4.05. Found: C, 69.75; H, 7.38; N, 3.88. Also the quaternary methiodide, m.p. 179–180° (from ethanol-ether). *Anal.* Calcd. for $C_{21}H_{28}INO_2$ C, 55.88; H, 5.81; N, 3.10. Found: C, 55.89; H, 6.05; N, 3.20. [l] Added two moles of benzyl chloride before reaction of one mole of the acid with two moles of sodium hydride was complete. [m] M.p. 83–85°. P. Ramart, *Bull. soc. chim., France*, [4] 35, 196 (1924) reported m.p. 85° for this ester. [n] B.p. 172–178° (0.4 mm.); n_D^{25} 1.5860. Ramart[m] reported b.p. 205–207° (2 mm.) for this compound. [o] B.p. 147–149° (1.0 mm.), n_D^{25} 1.5551; this was hydrolyzed in 85% yield to diphenylpropionic acid, m.p. 173–174°. [p] B.p. 180–190° (1.1–1.2 mm.), n_D^{25} 1.5816. *Anal.* Calcd. for $C_{32}H_{32}O_2$: C, 83.60; H, 6.71. Found: C, 83.47; H, 7.01. [q] Reaction mixture went to neutrality, but 90% of the ethyl diphenylacetate was recovered. Elimination of hydrogen chloride from the chloride must have occurred [r] Acylating agent. [s] M.p. 145–146°. R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, 69, 2325 (1947) reported a 42% yield, m.p. 148–149°, by treatment of the potassium derivative (from potassium amide in liquid ammonia) of ethyl diphenylacetate with benzoyl chloride. [t] M.p. 83–84° (from ethanol). *Anal.* Calcd. for $C_{24}H_{22}O_4$: C, 76.98; H, 5.92. Found: C, 76.62; H, 6.04. [u] M.p. 103–104°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92; O, 13.43. Found: C, 80.41; H, 6.07; O, 13.50. W. Wislicenus and W. Mocker, *Ber.*, 46, 2772 (1913) prepared the ethyl ester in "good" yield by alkylation with methyl iodide using potassium ethoxide in ether-alcohol solution. [v] M.p. 92–94°. J. B. Conant and B. S. Garvey, *J. Am. Chem. Soc.*, 49, 2599 (1927) reported m.p. 96–97° for this compound prepared by esterification of the acid formed by carbonation of the potassium salt of 9-methylxanthene. It does not appear to have been made previously by methylation of methylxanthene-9-carboxyate. [w] Based on unrecovered starting material. 60% conversion. [z] Isolated as the oxalate salt, m.p. 126–127° (from ethanol). *Anal.* Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.25; H, 5.66; N, 4.20. Also the hydrochloride hemihydrate, m.p. 136–137° (from *i*-propyl alcohol–ether). *Anal.* Calcd. for $C_{19}H_{18}ClN.1/2H_2O$: C, 74.87; H, 6.28; N, 4.60. Found: C, 74.71; H, 6.24; N, 4.69.

days, a 34% yield of cyanophenylacetaldehyde was isolated. However, none of this by-product could be found after only five hours. Since most alkylation reactions in dimethylformamide would be complete in five to twenty hours at room temperature, their competitive position relative to the formylation reaction should be quite favorable. As expected, sodio-diphenylacetonitrile was not formylated by dimethylformamide even after standing for a week.

To provide as broad a picture as possible of the utility of the sodium hydride[29]–dimethylformamide system, many active methylene compounds, representing a wide range of acidities, were tested for their ease of conversion to corresponding sodium derivatives by means of this reagent. The results, which may be useful to anyone contemplating alkylation of a type not included in any of the tables, are given at the end of the experimental section.

EXPERIMENTAL[30]

General procedure for alkylations with sodium hydride in dimethylformamide. One mole of sodium hydride[31] was suspended in 200 to 400 ml. of dry dimethylformamide[32] in a three-neck flask fitted with a thermometer, stirrer, reflux-condenser (drying-tube), nitrogen inlet tube, and dropping funnel. One mole of the active methylene compound (dissolved in a minimum of dry dimethylformamide, if solid) was added dropwise with stirring under a dry nitrogen atmosphere. The internal temperature was maintained below 40–50° by regulating the rate of addition, or by cooling in ice.

After formation of the sodium derivative was complete, as evidenced by disappearance of the sodium hydride or by cessation of hydrogen evolution, 1.0 to 1.2 moles of alkylating agent was added portionwise. Approximately one fourth of the total was added in one portion with stirring under nitrogen and if no exothermicity resulted the reaction mixture was slowly warmed on the steam bath. At 10 or 15° increments the steam bath was removed to enable detection of any heat of reaction. If exothermicity developed the steam bath was not replaced and the reaction was controlled by the rate of addition of the rest of the alkylating agent. If no heat of reaction developed even at maximum steam-bath temperature, the rest of the alkylating agent was added in two portions, allowing enough time between additions to ensure against possible loss of temperature control.

The reaction was then completed by further heating on the steam bath until it had proceeded to neutrality (moist test paper). In some cases where neutrality was not achieved, progress of the reaction was measured by periodic titration of pipeted aliquots of the reaction mixture. No appreciable change in titer obviously indicated the futility of further heating at 100°. In a few such cases continued heating at higher temperatures up to reflux (150°) sustained the reaction. However, except when alkyl chlorides were used alkylations in dimethylformamide were benefited little by heating longer than 6 or 7 hr. or hotter than 100°.

(29) Because they react with the solvent, neither metallic sodium nor sodium amide can be used in dimethylformamide.

(30) Melting points are uncorrected.

(31) The 50% mineral oil suspension of sodium hydride could be used unless it turned out that the mineral oil complicated purification of the product. Nearly all of the hydride reactions reported in the tables were carried out when unsupported sodium hydride was still available commercially.

(32) Dried by distillation at atmospheric pressure.

When reaction was complete, most of the solvent was removed by distillation under water-pump vacuum[33] and the residue was partitioned between water and ether. If the aqueous layer was not already neutral, the ether extract was washed with water and then dried over anhydrous magnesium sulfate. After filtration and removal of the ether by distillation, the residual product was purified by fractionation or recrystallization. More specific conditions for particular alkylations are indicated in the tables.

Alkali metal salts of ethyl acetoacetate from alkali hydroxides. Potassium salt. A solution of 139.5 g. (1.05 moles) of ethyl acetoacetate in 1 l. of benzene was placed in a 3-l. three-neck flask fitted with a stirrer, thermometer, nitrogen inlet tube, reflux condenser, and a water trap.[34] The solution was heated to reflux with stirring under an atmosphere of nitrogen, and 66 g. (1.0 mole) of 85% potassium hydroxide pellets (15% water) was added in seven or eight approximately equal portions at 0.5-hr. intervals. A typical run was as follows, in which the first number in each parenthesis represents the total weight of hydroxide added, and the second indicates the milliliters of water trapped as of that 30-min. interval: (7.0, 0), (15, 2.6), (26.5, 5.5), (37.3, 10.5), (47.0, 14.6), (57.0, 18.3), (66.0, 22.8), (66.0, 25.7), (66.0, 27.5). After each addition of alkali, an exothermic reaction ensued and as water of neutralization formed, the vapor reflux temperature suddenly decreased slightly (benzene-water azeotrope) and then slowly rose to the normal benzene reflux temperature as the water was trapped. In 4 hr., salt formation was essentially complete. The evolution of nearly the theoretical amount of water (27.5 ml. *vs.* 27.9 ml.) taken together with the observation that the reflux temperature always reverted to normal (*i.e.*, no benzene-ethanol azeotrope was formed), showed that ester hydrolysis was essentially absent under these conditions. However, when the acetoacetic ester was added to the potassium hyroxide stirred in refluxing benzene, water evolution was not quantitative and refractory foaming of the mixture adversely complicated the procedure.

In the alkylations reported in Table II, the benzene was removed by distillation on the steam bath (last traces were eliminated under water-pump vacuum), and replaced by the designated solvent in the desired amount. Products were isolated according to the above general procedure.

The potassium salt prepared by this method appeared to exist in both a crystalline benzene-insoluble form and in a glassy, noncrystalline, soluble form. In one run (1-mole quantity), the crystalline modification was filtered from the hot solution and washed with more hot benzene. Drying gave 44 g. of light tan powder, m.p. 150–152° (softening at 145°). This appeared to be quite pure potassium salt of ethyl acetoacetate.

Anal. Calcd. for $C_6H_9O_3K$: C, 42.83; H, 5.39; K, 23.24. Found: C, 42.60; H, 5.59; K, 23.42.

Sodium salt. When 40 g. (1 mole) of sodium hydroxide (pellets) was substituted for the potassium hydroxide in the above procedure, 17.7 ml. (theory = 18 ml.) of water was trapped in 4 hr. Filtration of the hot reaction mixture gave 32 g. of white powder, m.p. 165–167°. From the cooled filtrate, there crystallized 20 g. of pure sodium salt of ethyl acetoacetate, m.p. 178–180° (softening at 170°).

Anal. Calcd. for $C_6H_9O_3Na$: C, 47.37; H, 5.96; Na, 15.12. Found: C, 47.20; H, 6.33; Na, 15.04. The infrared spectrum (potassium bromide) showed strong absorption at 6.10 μ but none in the normal ester region (5.7–5.8 μ).

The identical salt was obtained either with sodium hydride in benzene or with sodium metal in dry ether. In moist air it rapidly formed a hemihydrate, m.p. 117–121°.

Anal. Calcd. for $C_6H_9O_3Na.1/2H_2O$: C, 44.80; H, 6.27. Found: C, 45.27; H, 6.49.

This hemihydrate readily reverted to the anhydrous salt (m.p. 178–180°) in a desiccator (calcium chloride) at room temperature.

As with the potassium salt, pure crystalline sodium salt was not used in the alkylations reported in Table II. For each run, sodium salt was prepared in the usual way, benzene was removed by distillation and replaced by the desired solvent.

Alkaline earth metal salts of ethyl acetoacetate. Calcium salt. From 450 ml. of ethyl acetoacetate and 98.3 g. (1.755 moles) of freshly calcined calcium oxide in 1200 ml. of benzene was obtained according to the method of Hackman,[19] 443 g. (85%) of calcio-acetoacetic ester, m.p. 224–226°.

Anal. Calcd. for $C_{12}H_{18}O_6Ca$: C, 48.31; H, 6.08. Found: C, 47.90; H, 5.88.

This material was used for all of the calcium salt reactions listed in Table II. It was soluble in warm dimethylformamide.

Magnesium salt. In similar manner from 550 ml. of ethyl acetoacetate and 65 g. (1.615 moles) of freshly calcined magnesium oxide in 1300 ml. of benzene was obtained 446 g. (98% yield based on magnesium oxide) of the magnesium salt of ethyl acetoacetate as a white powder m.p. 250–252° dec., reported[35] m.p. 240° dec.

Anal. Calcd. for $C_{12}H_{18}O_6$ Mg: C, 51.01; H, 6.42. Found: C, 50.93; H, 6.21.

This salt was soluble in hot (100°) dimethylformamide and insoluble in hot water in which it appeared to be stable.

Barium salt. A suspension of 63.1 g. (0.2 mole) of barium hydroxide octahydrate (Analytical Reagent Grade) in 400 ml. of benzene was stirred and refluxed in the apparatus described above for the preparation of the potassium salt. In 1 hr. 25 ml. (corresponding to $7H_2O$) of water was trapped and in 5 hr. 28 ml. (theory for $8H_2O$ = 28.8 ml.) was obtained. The solid cake was broken up, and to the refluxing stirred suspension (nitrogen atmosphere) was added dropwise over a period of 1 hr., 52 g. (0.4 mole) of ethyl acetoacetate. A gelatinous precipitate that formed during the addition gradually dissolved as water was eliminated. After completion of the addition, stirring and refluxing were continued for 2 more hr. at the end of which 7.0 ml. (theory = 7.2) more water (35 ml. in all) had been collected, and a pale yellow solution of the barium salt was formed. Even on cooling it remained dissolved.

For the alkylations reported in Table II, the benzene was removed by distillation to give a brown glassy residue. Addition of a little cold dimethylformamide to this salt gave a solid complex which slowly dissolved on heating in excess dimethylformamide.

In working up some of the reaction mixtures obtained by alkylation of the alkaline earth salts (especially the magnesium salt), warming the residue (after removal of dimethylformamide) with dry ethanolic hydrogen chloride decomposed unchanged salt without hydrolyzing the ester. This facilitated partitioning of the products between ether and water (see general procedure for alkylations with sodium hydride in dimethylformamide).

Potassium salt of diethyl malonate. A mixture of 26.4 g. (0.40 mole) of 85% potassium hydroxide (pellets), 67 ml. (0.44 mole) of diethyl malonate and 400 ml. of benzene was stirred and refluxed under nitrogen for 22 hr. Water, which was trapped in the usual way, was evolved as follows: 5 ml. in 30 min., 7.2 ml. in 1 hr., and 10.5 ml. in 22 hr. (theory = 11.1 ml.). Although appreciable quantities of the salt remained undissolved in benzene, filtration, washing, and drying yielded an impure product, m.p. 240–245° after darkening at 190–200°.

Anal. Calcd. for $C_7H_{11}O_4K$: C, 42.40; H, 5.59; K, 19.72. Found: C, 38.52; H, 5.13; K, 22.14.

(33) When the product was relatively volatile, (*e.g.*, methylacetoacetic ester, b.p. 180°) it was separated from solvent by fractional distillation.

(34) Similar to the one described in E. C. Horning, *Org. Syntheses*, **Coll. Vol. III**, 382 (1955).

(35) M. Conrad, *Ann.*, **188**, 269 (1877).

As usual, the crude salt obtained after removal of the benzene was used in the dimethylformamide alkylation (Table III).

Neither the sodium nor the barium salt of diethyl malonate could be prepared in this way. Much less than the theoretical amount of water was trapped in each case. Indeed, when sodium hydroxide was substituted for potassium hydroxide in the above procedure, the temperature of the refluxing vapors decreased to 72° as a consequence of hydrolysis (benzene-ethanol azeotrope).

Cyanophenylacetaldehyde. To a stirred suspension of 2.6 g. (0.11 mole) of sodium hydride in 40 ml. of dry dimethylformamide was added 11.7 g. (0.1 mole) of phenylacetonitrile over a period of 5–10 min. The temperature was not allowed to exceed 30°. The red solution was stirred at room temperature for 2 days and then allowed to stand without stirring for 3 more days.

The solvent was removed by distillation at the water pump, the red residue was taken up in cold water and acidified with 10 ml. of cold concd. hydrochloric acid. The precipitated greenish yellow oil was taken up in ether, washed with water to neutrality and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave 12 g. of green semisolid product. Trituration with benzene and collection at the filter gave 5.0 g. (34%) of cyanophenylacetaldehyde, m.p. 150–155°. Two recrystallizations from dilute aqueous ethanol gave colorless crystals, m.p. 157–158°, reported[36] m.p. 158°.

Anal. Calcd. for C_9H_7NO: 74.47; H, 4.86. Found: C, 74.25; H, 4.97.

When the above reaction was worked up after only 5 hr., phenylacetonitrile was recovered nearly quantitatively. Also, treatment of diphenylacetonitrile with sodium hydride in dimethylformamide for 1 week under the above conditions led to a complete recovery of starting material.

Reaction of active methylene compounds with sodium hydride in dimethylformamide. In order to determine qualitatively this type of reactivity, the active methylene compounds were added individually to a suspension of sodium hydride (free of mineral oil dispersant) in dimethylformamide. Reactivity was judged as rapid, slow, or negative by the rate of evolution of hydrogen, detectable exothermicity, and rate of color development. The following compounds reacted rapidly at room temperature to give colored solutions (y = yellow r = red, g = green); $CH_3COCH_2COOC_2H_5$(y), $CH_2(COOC_2H_5)_2$ (y), $CH_2(CN)COOC_2H_5$(y), $C_6H_5CH_2CN$(r), $(C_6H_5)_2CHCN$(r), $C_6H_5CH_2COCH_3$(r), $C_6H_5COCH_3$(r), cyclohexanone (y→r), homophthalic anhydride (y), *N*-cyanomethylphthalimide (r), indene (g). Nitromethane reacted rapidly but gave a white precipitate insoluble even in hot dimethylformamide. The following three substances reacted rapidly only in hot (95–100°) dimethylformamide: $(C_6H_5)_2CHCOOC_2H_5$(y), $C_6H_5CH(C_2H_5)COOCH_2CH = CH_2$(g), *o*-nitrotoluene (r). The following reacted slowly even when heated: $CH_3COOC_2H_5$(y), fluorene (r), ethyl *o*-toluate (y). The following gave little or no noticeable evidence of salt formation even when heated: acetonitrile, propionitrile, α-picoline, γ-picoline, quinaldine, diphenylmethane, triphenylmethane, N,N-dimethyldiphenylacetamide, N,N-pentamethylenediphenylmethanesulfonamide. It is interesting to note that on long standing with sodium hydride in dimethylformamide, diphenylmethane gave a bright lavender color which was rapidly discharged on shaking with air.

Acknowledgments. The authors are indebted to Mr. E. F. Shelberg for the microanalyses and to Mr. W. F. Washburn for the infrared spectrum.

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(36) M. F. Bodroux, *Bull. soc. chim. France*, [4] 7, 848 (1910).

[CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Reactions of Hydrogen Peroxide. VI. Alkaline Epoxidation of Acrylonitrile

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Received April 20, 1960

Reaction of equimolar quantities of acrylonitrile and hydrogen peroxide at *p*H 7.0–7.5 gave glycidamide, a new epoxyamide, in 65–70% yield by titration for oxirane oxygen. An intramolecular rearrangement of peroxyacrylimidic acid is proposed to account for the stoichiometry observed. Evidence for peroxyacrylimidic acid as an intermediate was secured when added cyclohexene underwent epoxidation. α-Phenyl-*trans*-cinnamonitrile, on treatment with alkaline hydrogen peroxide, gave a mixture which included as the major product the epoxyamide which would be expected to result from an intramolecular epoxidation.

The successful epoxidation of acrolein[1] and diethyl ethylidenemalonate[2] by means of hydrogen peroxide under conditions of controlled *p*H indicated that α,β-unsaturated nitriles might respond to the same technique to give epoxy*nitriles*. Earlier,[3,4] treatment of aryl-substituted acrylonitriles with excess hydrogen peroxide in the presence of sodium carbonate had resulted in the formation of epoxyamides rather than nitriles.

Acrylonitrile was selected for an initial study of this reaction. It had been treated earlier with hydrogen peroxide under strongly alkaline conditions to give only "resinous products".[3]

When acrylonitrile and hydrogen peroxide were allowed to react in aqueous solution at *p*H 7.0–7.5 and 35°, glycidamide (I) was produced in 65–70% yield as determined by titration of the reaction

I

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