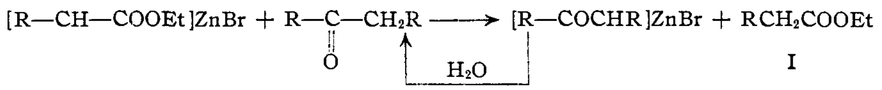
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY AND THE OHIO STATE UNIVERSITY]

Some Observations on the Reformatsky Reaction

BY ALLEN S. HUSSEY AND MELVIN S. NEWMAN

In previous work, it has been shown that low yields in the Reformatsky reaction may be caused by the side-reaction of enolization. The recovery of unreacted ketone and reduced ester, I, from reactions in which a mole of zinc and a mole of bromoester are consumed has been explained as shown below[1]:



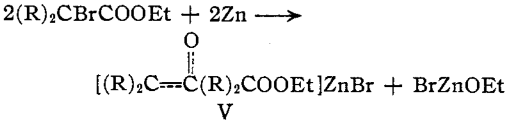
$$[\mathrm{R{-}CH{-}COOEt}]\mathrm{ZnBr} + \mathrm{R{-}\underset{\underset{\textstyle O}{\|}}{C}{-}CH_2R} \longrightarrow [\mathrm{R{-}COCHR}]\mathrm{ZnBr} + \underset{\textstyle \mathrm{I}}{\mathrm{RCH_2COOEt}} \quad (1)$$

H_2O

However, the yield of Reformatsky product may often be greatly increased by an excellent procedure involving the use of large excesses of zinc and bromoester.[2,3] The side reactions of bromoester with zinc to form halogenated β-ketoester and coupling products have been suggested[4] in explanation of the improved yield of Reformatsky product under the above[2] conditions. We have undertaken a study of the Reformatsky reaction using 5,8-dimethyl-1-tetralone[5] with ethyl bromoacetate, α-bromopropionate,[6] and α-bromoisobutyrate and have examined the reaction mixtures for end-products of side-reactions involving bromoester. In most experiments 60-80% of the bromoester and 85–95% of the ketone have been accounted for. We have found that a complex self-condensation of bromoesters to form non-halogenated β-ketoesters, $(R)_2CHCOC(R)_2COOEt$, II, often occurs but we were unable to detect any halogenated β-ketoester or coupled product.[4]

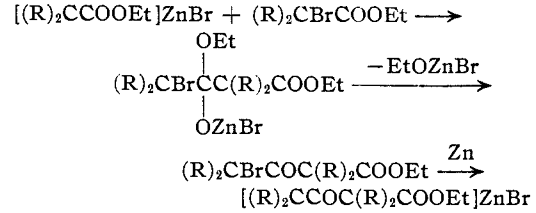
When an excess of bromoester and zinc was used, the yield of Reformatsky product, based on ketone, was increased from 25% to 85% with ethyl bromoacetate and from 17% to 82% with ethyl α-bromopropionate. No Reformatsky product was obtained with ethyl α-bromoisobutyrate. One mole of zinc was consumed for each mole of bromoester used and approximately the same amount, 10–15%,[7] of reduced ester, I, was isolated with all three bromoesters. In addition, 15% of ethyl acetoacetate, 35% of ethyl α-propionylpropionate and 69% of ethyl α-isobutyrylisobutyrate were isolated from reactions involving an excess of the respective bromoesters.[7] Especially noteworthy is the fact that while ethyl bromoacetate reacts with zinc very slowly in the absence of carbonyl compounds,[1] ethyl α-bromopropionate reacted vigorously with zinc in the absence of ketone to give 16% of I and 39% of II. Under the same conditions, ethyl α-bromoisobutyrate gave traces of I and 65% of II.[8] The results are summarized in Table I.

The formation of non-halogenated β-ketoesters, II, is quite interesting. There are many reports of the formation of such compounds, usually in low yield, from reactions of α-haloesters with magnesium and zinc.[8,9] We have determined that the over-all stoichiometry is as given by equation 2.



$$2(\mathrm{R})_2\mathrm{CBrCOOEt} + 2\mathrm{Zn} \longrightarrow$$
$$\underset{\textstyle \mathrm{V}}{[(\mathrm{R})_2\mathrm{C}{=}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}(\mathrm{R})_2\mathrm{COOEt}]\mathrm{ZnBr}} + \mathrm{BrZnOEt} \quad (2)$$

One possible reaction path is indicated below.



$$[(\mathrm{R})_2\mathrm{CCOOEt}]\mathrm{ZnBr} + (\mathrm{R})_2\mathrm{CBrCOOEt} \longrightarrow$$
$$(\mathrm{R})_2\mathrm{CBr}\overset{\overset{\textstyle \mathrm{OEt}}{|}}{\underset{\underset{\textstyle \mathrm{OZnBr}}{|}}{\mathrm{C}}}(\mathrm{R})_2\mathrm{COOEt} \xrightarrow{-\mathrm{EtOZnBr}}$$
$$(\mathrm{R})_2\mathrm{CBrCOC}(\mathrm{R})_2\mathrm{COOEt} \xrightarrow{\mathrm{Zn}} [(\mathrm{R})_2\mathrm{CCOC}(\mathrm{R})_2\mathrm{COOEt}]\mathrm{ZnBr}$$

The importance of this self-condensation reaction increases in the order $CH_2BrCOOEt < CH_3CHBrCOOEt < (CH_3)_2CBrCOOEt$ as shown by the reactions of the esters in the absence of ketone. In view of the improved yield of ethyl α-propionylpropionate in the presence of acetomesitylene (compare experiment 12 with 6 and 7, Table I), even though the latter seems to play no part in the reaction, further studies are in order.

The ways in which reduced ester, I, may be formed are also of interest. Enolization, equation 1, offers one explanation. However, in view of the fact that appreciable amounts of ethyl propionate are formed in the reaction of ethyl α-bromopropionate with zinc in the absence of ke-

---

[1] Newman, THIS JOURNAL, **64**, 2131 (1942).

[2] Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).

[3] That large excesses of zinc and bromoester do not always give better yields is shown by the fact that with 4-keto-1,2,3,4-tetrahydrophenanthrene a single addition of a slight excess of zinc and methyl or ethyl bromoacetate gives as good a yield as that reported by Bachmann and Edgerton, *ibid*, **62**, 2970 (1940). Newman, unpublished observations.

[4] Shriner, "The Reformatsky Reaction" in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 4.

[5] Ruzicka and Waldmann, *Helv. Chim. Acta*, **15**, 907 (1932); Barnett and Sanders, *J. Chem. Soc.*, 434 (1933).

[6] Newman and Hussey, THIS JOURNAL, **69**, 3023 (1947).

[7] Yield based on bromoester used.

[8] Zeltner, *Ber.*, **41**, 589 (1908), obtained 67% of ethyl α-isobutyrylisobutyrate from the reaction of magnesium with ethyl α-bromoisobutyrate.

[9] Fittig, Daimler and Keller, *Ann.*, **249**, 184 (1888); Hann and Lapworth, *Proc. Chem. Soc.*, **19**, 189 (1903); Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 110 (1904); Stolle, *Ber.*, **41**, 854 (1908); Rottinghen and Wenzel, *Monatsh.*, **34**, 1867 (1913).

TABLE I

	Procedure	Ketone used		Zinc consumed		Bromoester[a] used		Ketone recovered		Reformatsky product		Reduced ester		β-Keto-ester	
		g.	moles	g.	moles	g.	moles	g.	%	g.	%[b]	g.	%[c]	g.	%[c]
1	I	40.0	0.23	45	0.69	115	(A) 0.69	2.3	6	48.2	86	6.3	10	6.4	14
2	I	21.0	.12	24	.37	60	(A) 0.36	0	0	24.8	85	4.1	13	4.0	17
3	II	17.7	.10	6.5	.10	16.7	(A) 0.10	11.2	63	7.0	28	<1		[e]	
4	II	30.0	.17	10.6	.16	28.7	(A) 0.17	20.8	67	9.9	24	<1		[e]	
5	I	50.0	.29	57	.87	160	(P) 0.83	4.0	8	60.4	81	13.3	16	20.0	31
6	I	97.7	.56	107	1.63	300	(P) 1.65	9.6	10	116	82	23.8	14	48.3	37
7	I	...	..	27	0.42	80	(P) 0.44	...	..	...	..	6.7	16	12.8	39
8	II	165	.95	69	1.05	190	(P) 1.05	108	66	40.6	17	...	..	..	..
9	I	40.0	.23	46	0.70	135	(B) 0.69	36.1	90	0	0	12.3	18	43.1	67
10	I	32.6	.19	37	.56	110	(B) 0.56	27.0	83	0	0	8.2	12	37.0	71
11	I	...	..	44	.67	135	(B) 0.69	...	..	...	..	<1		41.6	65
12	I	44.4[d]	.27	46	.70	150	(P) 0.83	40.6	92	0	0	23.5	27	38.8	59

[a] Ethyl bromoacetate (A); ethyl α-bromopropionate (P); ethyl α-bromoisobutyrate (B). [b] Yield based on ketone. [c] Yield based on bromoester. [d] Acetomesitylene used as ketone. [e] A small amount (1–3 g.) of ethyl acetoacetate observed—exact amount not determined.

tone,[10] (experiment 7, Table I), other reactions must be involved. Perhaps an acid-base type reaction between organozinc intermediate and bromoester, as shown in equation 3, occurs.

$$[\mathrm{RCHCOOEt}]\mathrm{ZnBr} + \mathrm{RCHBrCOOEt} \longrightarrow \mathrm{RCH_2COOEt} + \underset{\mathrm{VII}}{[\mathrm{RCBrCOOEt}]\mathrm{ZnBr}} \quad (3)$$

It is noteworthy in this connection that no reduced ester is produced in the self-condensation of ethyl α-bromoisobutyrate, a bromoester which does not possess an acidic α-hydrogen, when this is treated with zinc in the absence of ketone (experiment 11, Table I).

A further possibility, also involving the acidity of the α-hydrogen of the bromoesters, is indicated in equation 4.

$$[\mathrm{RCOCHR}]\mathrm{ZnBr} + \mathrm{RCHBrCOOEt} \longrightarrow \mathrm{RCOCH_2R} + \underset{\mathrm{VII}}{[\mathrm{RCBrCOOEt}]\mathrm{ZnBr}} \quad (4)$$

The regeneration of starting ketone in this way may be another reason why improved yields of Reformatsky products are obtained when an excess of bromoester is used. We can present no evidence as to the fate of VII except to note that a certain amount of high-boiling material and tars is always formed. However, analogy for such an halogenated enolate is to be found in other reactions.[11,12]

It thus appears that the main reason why an excess of zinc and of bromoester improves the yield of Reformatsky product is because these reagents are supplied in amounts sufficient to compensate for the losses in the side-reactions, two of which are discussed above. It would be expected that unless a reactive ketone were used, little Reformatsky product would be obtained from reactions involving ethyl α-bromoisobutyrate, mainly because of the great tendency of this bromoester to undergo self-condensation with the formation of a β-ketoester. With the rather hindered ketone used in this study, the failure to obtain Reformatsky product with this bromoester is therefore not surprising.

Experimental[13]

Procedure I.—A threefold excess of bromoester and a large excess (usually five- to sixfold) of freshly washed, 20-mesh zinc were added in portions with a crystal of iodine over three to four hours to a refluxing ether–benzene solution of 5,8-dimethyl-1-tetralone,[4] (0.1–0.5 mole), according to the general Reformatsky procedure developed by Bachmann.[2] After hydrolysis solvent and volatile products were removed under reduced pressure and carefully fractionated through a ten-plate, packed column with a total condensation partial take-off head. In several experiments, solvent and volatile products were removed under reduced pressure prior to hydrolysis.

The residue remaining after removal of the solvent was heated to effect dehydration and then vacuum distilled. The distillate was saponified, and separated into neutral and acid fractions. From the former, unreacted ketone was recovered by distillation under reduced pressure. The acid fraction was esterified with ethanol using benzene to aid in driving to completion and the ethyl esters recovered by distillation under reduced pressure.

Procedure II.—A small excess, 1–10%, of freshly sanded zinc foil[14] and a crystal of iodine were added to a hot solution of 5,8-dimethyl-1-tetralone and 1–2% excess bromoester in anhydrous benzene. When the initial vigorous reaction had subsided, the mixture was refluxed gently for a total reaction time of one and one-half hours. The reaction mixture was worked up as described in Procedure I.

Ethyl α-5,8-Dimethyl-3,4-dihydro-1-naphthylacetate.—The crude ester from above was purified by distillation under reduced pressure, b. p. 133–137° at 0.5 mm., $n^{25}\mathrm{D}$ 1.5576.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.6; H, 8.3. Found: C, 78.7; H, 8.2.

On saponification, two acids were isolated by fractional crystallization from petroleum ether, b. p. 65–80° (Skellysolve B), and petroleum ether, b. p. 35–40° (Skellysolve

---

[10] The isolation of 15% of ethyl *n*-butyrate was cited as evidence of an enolization reaction in a previous article by Newman, THIS JOURNAL, **62**, 870 (1940). In view of the isolation of ethyl propionate from zinc and ethyl α-bromopropionate in the absence of ketone, the formation of reduced ester with bromoesters *other* than bromoacetates does not necessarily mean that enolization has occurred. Further evidence in support of the enolization side reaction is obtainable by consideration of experiments 10 and 11 of Table I, this paper. The evidence in reference 1 is also still valid.

[11] Conrad, *Ann.*, **209**, 241 (1881); Darzens, *Compt. rend.*, **151**, 883 (1910); Darzens and Delépine, *ibid.*, **203**, 1374 (1936); Darzens, *ibid.*, **139**, 1214 (1904); **141**, 766 (1905); Claisen, *Ber.*, **38**, 702 (1905); Scheibler and Tutundzitschk *ibid.*, **64**, 2916 (1931).

[12] It has been observed that about 79% of the theoretical amount of ammonia is evolved immediately on treating ethyl chloroacetate with sodamide. Newman and Magerlein, unpublished observations.

[13] All melting points corrected unless otherwise indicated. Microanalyses by Patricia Craig.

[14] Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

F). The less soluble form melted at 159.7–160.3° when purified for analysis; the second isomer melted at 107.9–108.6°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.7; H, 7.5. Found: (160° isomer) C, 77.5; H, 7.4; (108° isomer) C, 77.7; H, 7.4.

Reduced Esters, I.—Ethyl acetate distilled at 75–76° at 742 mm.; n^{24}D 1.3718; *p*-bromophenacyl acetate,[15] m. p. 85.4–86.4°, no depression with an authentic sample.

Ethyl propionate distilled at 96–97° at 748 mm.; *p*-bromophenacyl propionate,[16] m. p. 61.8–62.8°, no depression with an authentic sample.

Ethyl isobutyrate distilled at 108–110° at 746 mm.; n^{24}D 1.3889; *p*-bromophenacyl isobutyrate,[15] m. p. 75.6–76.4°, no depression.

β-Ketoesters, II.—Ethyl acetoacetate distilled at 87–89° at 24 mm.; n^{24}D 1.4183; 2,4-dinitrophenylhydrazone,[17] m. p. 95.0–96.2°, no depression.

Ethyl α-propionylpropionate distilled at 192–193° at 752 mm., and gave with phenylhydrazine 4-methyl-3-ethyl-1-phenyl-5-pyrazolone,[18] m. p. 110.0–111.8°.

Ethyl α-isobutyrylisobutyrate[8] distilled at 202–203° at 750 mm., n^{25}D 1.4252; semicarbazone,[19] m. p. 230–235°, uncor., dec.

Summary

The reactions of 5,8-dimethyl-1-tetralone with zinc and ethyl bromoacetate, α-bromopropionate and α-bromoisobutyrate are described.

The corresponding reduced esters and β-ketoesters were isolated and identified as end-products of side-reactions involving zinc and the α-bromoesters.

Mechanisms for the formation of these products are considered.

---

[15] Judefind and Reid, THIS JOURNAL, **42**, 1043 (1920).

[16] Moses and Reid, *ibid.*, **54**, 2101 (1932).

[17] Strain, *ibid.*, **57**, 760 (1935).

[18] Schroeter, *Ber.*, **49**, 2719 (1916).

[19] Zeltner and Reformatsky, *J. Russ. Phys.-Chem. Soc.*, **38**, 105 (1906); *Chem. Centr.*, **77**, II, 316 (1906).

EVANSTON, ILLINOIS
COLUMBUS, OHIO

RECEIVED JANUARY 16, 1948

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Pyrimido[4,5-b]pyrazines (Pteridines[1]). III. Pteridinemono- and -dicarboxylic Acids[2]

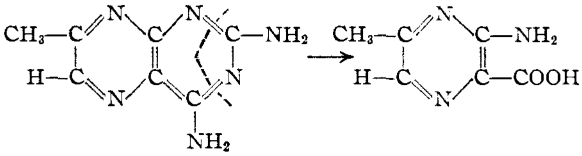
BY C. K. CAIN, M. F. MALLETTE[3] AND E. C. TAYLOR, JR.

Previous papers[4,5] from this Laboratory have reported the synthesis of a number of compounds containing the pteridine nucleus. These compounds have been for the most part those in which the pteridine nucleus has been substituted in the 2- and 4-positions by hydroxyl, amino or a combination of these two groups and in the 6- and 7-positions by hydrogen, alkyl, aryl or condensed ring groups. Because of the interesting biological properties of various pteridine derivatives, it seemed of interest to prepare derivatives in which one or two carboxyl groups occupy the 6- and 7-positions of the pteridine nucleus with the thought in mind that such substances might have different biological properties because of the presence of more reactive groups in these positions.

Table I lists the pteridinemono- and -dicarboxylic acids and their methyl esters which we have prepared together with significant data on their ultraviolet absorption spectra in solution. Three compounds previously reported by other investigators have been included for comparison.

The pteridinemono- and -dicarboxylic acids were prepared by oxidation of the corresponding methyl compounds with potassium permanganate according to standard procedures. Some of them proved extremely difficult to dry thoroughly for analysis as had been noted by Wittle, *et al.*,[6] in the case of Compound 3, Table I; accordingly, the acids were converted into the methyl esters by means of anhydrous methyl alcohol and dry hydrogen chloride. The methyl esters are crystalline compounds which may be purified by recrystallization and easily dried.

One of the compounds used for conversion to the acid by oxidation with potassium permanganate had been originally reported as 2,4-diamino-6-(or 7)-methylpteridine.[5] We have shown that the compound is the 7-methyl isomer by cleavage to 2-amino-6-methyl-3-pyrazinecarboxylic acid using the procedure of Weijlard, Tishler and Erickson.[8] These authors showed by the cleavage reaction that the condensation of 2,4-dihydroxy-5,6-diaminopyrimidine with methylglyoxal results in the formation of 2,4-dihydroxy-7-methylpteridine. They were unable to detect the presence of the 6-methyl isomer in the product. Similarly, Mowat, *et al.*,[7] have shown that 2-amino-4-hydroxy-7-methylpteridine results from



---

[1] The common name "pteridine" is used to refer to pyrimido-[4,5-b]pyrazine.

[2] The work presented in this paper was undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and was aided by a grant to Cornell University by the Nutrition Foundation, Inc., New York City. It represents a part of a collaborative project on "Newer Members of the B Group of Vitamins."

[3] Present address: Department of Chemistry, University of Wyoming, Laramie, Wyoming.

[4] Cain, Mallette and Taylor, THIS JOURNAL, **68**, 1996 (1946).

[5] Mallette, Taylor and Cain, *ibid.*, **69**, 1814 (1947).

[6] Wittle, O'Dell, Vandenbelt and Pfiffner, *ibid.*, **69**, 1786 (1947).

[7] Mowat, *et al.*, *ibid.*, **70**, 14 (1948).

[8] Weijlard, Tishler and Erickson, *ibid.*, **67**, 802 (1945).