Anal. Calcd. for $C_6H_3Br_2SO_2Cl$, Cl: 1.06. Found: 1.04.

2,4,6-Tribromobenzenesulfonchloride.—A mixture of 20 g. of 2,4,6-tribromobenzene, 30 cc. of chlorosulfonic acid and 30 cc. of sulfuryl chloride was heated at 100° for four hours. The reaction mixture was worked up by the same procedure as above. The yield was 15–19 g. (57–72%) of a buff colored product which melted at 63.5–64°.

2,4-Dinitrobenzenesulfonchloride.—Oxidative cleavage of 2,4,2′,4′-tetranitrodiphenyl disulfide by aqua regia according to the procedure previously described[1] yielded this sulfonchloride in 72% yields, m. p. 100–101°.

Attempted Preparation of 2,4,6-Trinitrobenzenesulfonchloride.—Attempts to prepare this compound by the action of phosphorus pentachloride alone, in a solution of xylene, and mixtures of it with phosphorus trichloride and oxychloride on the sodium salt of 2,4,6-trinitrobenzene sulfonate, prepared by the method of Willgerodt,[4] at various temperatures from 80–180°, were unsuccessful. The only product isolated was picryl chloride.

This sulfonchloride could not be prepared by the method used above for the 2,4-dinitrobenzenesulfonchloride because the reaction between picryl chloride and sodium disulfide gave only the hexanitrodiphenylsulfide. Variations in conditions failed to produce any disulfide. The action of potassium hydrogen sulfide on picryl chloride also gave the monosulfide and no disulfide or thiopicric acid.

The 2,4,6,2′,4′,6′-hexanitrodiphenylsulfide was produced in almost quantitative yields by the first reaction. It decomposed at 227–228°.

Anal. Calcd. for $C_{12}H_4O_{12}N_6S$; S, 7.01; Found: S, 7.03.

(4) Willgerodt, *J. prakt. Chem.*, **32**, 117 (1885).

Preparation of Sulfonanilides and N-Methyl Sulfonanilides.—The general method followed consisted in adding the powdered sulfonchloride to an excess of the amine at a temperature below 10° with vigorous stirring. The sulfonamides were washed with water, dilute acid and again with water. The solids were recrystallized from alcohol or glacial acetic acid and the liquids vacuum distilled. Table III summarizes the data on new compounds; the 2,4-dinitrosulfonanilide and methylanilide have been previously described.[1]

TABLE III

Compound	M. p., °C.	Solvent for crys.	Analyses, %	Calcd.	Found
$2,4\text{-}Br_2C_6H_3SO_2NHC_6H_5$	145.4–6.5	Alc.	N	3.59	3.63
$2,4\text{-}Br_2C_6H_3SO_2N(CH_3)C_6H_5$	Oil B. p. 210–214° (4 mm.)		N	3.46	3.47
$2,4,6\text{-}Br_3C_6H_2SO_2NHC_6H_5$	118	Alc.	N	2.99	3.20
$2,4,6\text{-}Br_3C_6H_2SO_2N(CH_3)C_6H_5$	148–8.5	HOAc	N	2.90	3.10
$2,4,6\text{-}(CH_3)_3C_6H_2SO_2NHC_6H_5$	108–9	Alc.	S	11.64	11.68
$2,4,6\text{-}(CH_3)_3C_6H_2SO_2N(CH_3)C_6H_5$	95–6	Alc.	S	11.07	10.92

Alkaline Hydrolysis.—The general procedure followed the same lines as previously described.[1] The yields of amines and temperatures of heating have been given in Table I. The time of heating varies from thirty minutes for the nitro compounds to four hours for the others.

Summary

A study of the alkaline cleavage of substituted benzene-sulfonanilides indicates that nitro groups are more effective in promoting the cleavage than bromo- or methyl groups. The results indicate that weight, size or steric hindrance effects are not factors in this cleavage.

URBANA, ILL. RECEIVED NOVEMBER 23, 1933

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of Organic Halides with Piperidine. IV. Bromo Esters

BY W. V. DRAKE AND S. M. MCELVAIN

The previous papers[1] of this series have shown (1) that the rate of reaction of various alkyl bromides with piperidine is in the order primary > secondary > tertiary, and (2) that primary bromides, in general, react with 2 moles of piperidine to give one mole of a tertiary amine and one mole of piperidine hydrobromide; tertiary bromides react with one mole of piperidine with the elimination of hydrogen bromide and the formation of unsaturated compounds; secondary bromides follow both of these reaction courses but, with the exception of cyclohexyl bromide, give considerably more of the tertiary amine than unsaturated compound.

(1) (a) Semb and McElvain, THIS JOURNAL, **53**, 690 (1931); (b) Howk and McElvain, *ibid.*, **54**, 282 (1932); (c) Drake and McElvain, *ibid.*, **55**, 1155 (1933).

It seemed desirable to extend this study to the bromo esters in order to ascertain what effect the presence of a carbethoxy group in the molecule would have on the rate and course of reaction of these three types of bromides. The present paper reports the results obtained from thirteen different bromo esters.

Experimental

Bromo Esters.—The α-bromo esters used were made by the reaction of ethyl alcohol with the α-bromo acid bromides which were obtained by the direct bromination of the acid bromides. Ethyl β-bromopropionate was prepared from ethylene cyanohydrin.[2] Ethyl γ-bromobutyrate and ethyl δ-bromovalerate were prepared by

(2) "Organic Syntheses," Coll., Vol. I, 1932, p. 241.

previously described procedures.[3] Ethyl β-bromoisobutyrate was prepared by the addition of hydrogen bromide to ethyl α-methylacrylate.[4] The esters of the type $CH_3CHBr(CH_2)_nCOOC_2H_5$ have been described[5] recently.

General Procedure.—The rate and the course of the reaction for each of the bromo esters was determined by the procedure described in the first paper[1a] of the series except that carbon bisulfide[1c] instead of phenyl isocyanate was used for the determination of the unreacted piperidine. A ratio of 0.02 mole of piperidine to 0.01 mole of bromo ester was used in each case. The rates of reaction of the various bromo esters with piperidine at 90° are summarized in Table I.

TABLE I

RATE OF REACTION BETWEEN PIPERIDINE AND VARIOUS BROMO-ESTERS AT 90°

	Bromo ester Y = $COOC_2H_5$	% reaction in hrs. 0.25	1	2	4	8	64	144	168
1	$BrCH_2Y$	81.8	87.5	89.8	90.2				
2	CH_3CHBrY	43.5	70.4	80.0	87.2				
3	C_2H_5CHBrY	15.9	36.6	49.6	..	74.9			
4	$(CH_3)_2CBrY$	4.4	..	..	..	16.4[a]	57.5	73.8	
5	$Br(CH_2)_2Y$	97.5	..	..	..	98.0			
6	$Br(CH_2)_3Y$	43.9	73.5	81.5	..	93.7			
7	$Br(CH_2)_4Y$	36.1	64.9	75.3	83.9	90.7[b]			
8	$BrCH_2CH(CH_3)Y$	88.6[c]	95.6	96.8	..	97.9	..	99.0	
9	$CH_3CHBrCH_2Y$	94.6	..	..	..	96.9			
10	$CH_3CHBr(CH_2)_2Y$	4.6					66.5	84.0	
11	$CH_3CHBr(CH_2)_3Y$	5.9	..	..	..	..	65.9	82.7	
12	$CH_3CHBr(CH_2)_4Y$	..	3.0	..	..	..	52.0	66.6	69.8
13	$CH_3CHBr(CH_2)_5Y$	..	2.4	..	..	..	51.5	65.5	68.9

[a] 25.1% in 16 hr.; 37.9% in 32 hr. [b] 92.6% in 12 hr. [c] 95.7% in 0.5 hr.

TABLE II

THE COURSE OF THE REACTION BETWEEN PIPERIDINE AND CERTAIN BROMO-ESTERS AT 90°

Run	Bromo ester Y = $COOC_2H_5$	Reaction time, hr.	A % Reaction,	B Moles × 10^2 piperidine HBr	C Moles × 10^2 unreacted piperidine	D Moles × 10^2 amine calcd. 2 − (B + C)	E Moles × 10^2 unsatd. cpd. B − D	F Moles × 10^2 amine HCl isolated
1	$BrCH_2Y$	4	90.2	0.902	0.200	0.898	+0.002	0.674
2	CH_3CHBrY	4	87.2	.872	.166	.962	− .090	.741
3	C_2H_5CHBrY	8	74.9	.749	.452	.799	− .050	.613
4	$(CH_3)_2CBrY$	144	73.8	.738	.540	.622	+ .116	.577[a]
5	$Br(CH_2)_2Y$	0.25	97.5	.975	.183	.842	+ .133	...
6	$Br(CH_2)_3Y$	8	98.0	.980	.048	.973	+ .006	.800
7	$Br(CH_2)_3Y$	8	93.7	.937	.139	.924	+ .013	.800
8	$Br(CH_2)_4Y$	12	92.6	.926	.102	.972	− .046	.800
9	$BrCH_2CH(CH_3)Y$	6	97.1	.971	.733	.296	+ .675	.082
10	$BrCH_2CH(CH_3)Y$	144	99.0	.990	.440	.570	+ .420	.432
11	$CH_3CHBrCH_2Y$	0.25	94.6	.946	.819	.235	+ .711	.129
12	$CH_3CHBrCH_2Y$	8	96.9	.969	.386	.645	+ .324	.550
13	$CH_3CHBr(CH_2)_2Y$	144	83.9	.839	.308	.853	− .014	.740
14	$CH_3CHBr(CH_2)_3Y$	144	82.7	.827	.342	.831	− .004	.747
15	$CH_3CHBr(CH_2)_4Y$	168	69.8	.698	.564	.738	− .040	.594
16	$CH_3CHBr(CH_2)_5Y$	168	68.9	.689	.580	.731	− .042	.556

[a] This hydrochloride is the salt of ethyl β-piperidinoisobutyrate since it is identical with the one isolated in runs 9 and 10 from β-bromoisobutyric ester.

In Table II the data indicating the course of the reaction are summarized. The values in columns A and B of this table were determined from the amount of piperidine hydrobromide which precipitated in the reaction tube. Values in column C represent the amount of unreacted piperidine as determined by precipitation with carbon bisulfide. Column C shows the calculated amount of tertiary amine formed, assuming that the piperidine originally put into the reaction and not represented in columns B and C had reacted to form tertiary amine. There was a possibility that some of this piperidine had been consumed in amide formation with the carbethoxy group, but the purity of the hydrobromide of column B and the fact that no piperidine could be obtained from the hydrolysis of the residue of the petroleum ether solution, after the unreacted piperidine and tertiary amine had been removed, indicated that no detectable amount of amide formation had taken place. This conclusion was confirmed when ethyl acetate was heated with an excess of piperidine for four hours at 90° without a solvent and the reactants recovered unchanged. In column E positive values < 0.1 mole and all negative values are without significance and may be ascribed to errors in the determination of the values in columns B and C. Column F shows the amounts of the tertiary amine hydrochlorides actually isolated by precipitation from the petroleum ether solution with dry hydrogen chloride after the unreacted piperidine had been removed. It is believed that the differences between corresponding values of columns D and F are due, in large part, to the losses associated with the isolation and weighing of the tertiary amine hydrochloride. All values in Tables I and II represent an average of at least two determinations.

The formulas, melting points and analyses of the hydrochlorides of the various piperidino esters are summarized in Table III.

TABLE III

HYDROCHLORIDES OF VARIOUS PIPERIDINO ESTERS

Structure of base Y = $COOC_2H_5$ N = $C_5H_{10}N$	Formula, hydrochloride	M. p., °C. uncorr.	Analyses, Cl, % Calcd.	Found
N—CH_2Y	$C_9H_{18}O_2NCl$	130–1	17.09	17.28
$CH_3CH(N)$—Y	$C_{10}H_{20}O_2NCl$	131–2	15.99	15.95
$C_2H_5CH(N)$—Y	$C_{11}H_{22}O_2NCl$	113–4	15.04	14.93
N—$(CH_2)_2$—Y	$C_{10}N_{20}O_2NCl$	163–4	15.99	16.29
N—$(CH_2)_3$—Y	$C_{11}H_{22}O_2NCl$	128–9	15.04	15.20
N—$(CH_2)_4$—Y	$C_{12}H_{24}O_2NCl$	154–5	14.21	14.31
N—$CH_2CH(CH_3)Y$	$C_{11}H_{22}O_2NCl$	134–5	15.04	15.32
$CH_3CH(N)CH_2Y$	$C_{11}H_{22}O_2NCl$	177–8	15.04	15.18
$CH_3CH(N)(CH_2)_2Y$	$C_{12}H_{24}O_2NCl$	128–9	14.21	14.36
$CH_3CH(N)(CH_2)_3Y$	$C_{13}H_{26}O_2NCl$	135–6	13.45	13.62
$CH_3CH(N)(CH_2)_4Y$	$C_{14}H_{28}O_2NCl$	121–2	12.77	12.91
$CH_3CH(N)(CH_2)_5Y$	$C_{15}H_{30}O_2NCl$	116–7	12.15	12.26

Discussion of Experimental Results

With the exceptions which are discussed below the behavior of the various types of bromo esters appears to be in line with that of the alkyl bromides, *i. e.*, the order of reactivity as determined by the amount of piperidine hydrobromide produced

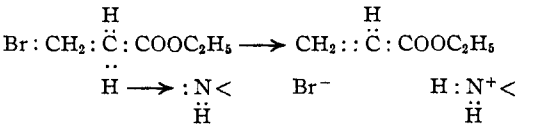
(3) Prill and McElvain, THIS JOURNAL, **55**, 1237 (1933).
(4) Ruzicka, *Helv. Chim. Acta*, **2**, 152 (1919).
(5) Lease and McElvain, THIS JOURNAL, **55**, 806 (1933).

in a given time is primary > secondary > tertiary.[6] There is, however, a general activating effect of the carbethoxy group which is quite marked when this group is close to the halogen and persists even when the halogen is in the ζ-position (*cf.* amount of reaction in Table I of the esters $CH_3CHBr(CH_2)_nCOOC_2H_5$ after 144 hr. and the value of 25.9% for secondary butyl bromide[1a] for the same time and reaction temperature).

The behavior of those esters in which the halogen occupies the β-position is interesting. For the simple metathetical reaction, RCl + KI ⟶ RI + KCl, Conant and Kirner[7] found that the relative reactivity (compared to *n*-butyl chloride as unity) of the members of a series of esters of the type $Cl(CH_2)_nCOOC_2H_5$ was 2800, 1.61, 1.65 and 1.35 where *n* is 1, 2, 3 and 4, respectively, *i. e.*, ethyl chloroacetate was about 1700 times as reactive as ethyl β-chloropropionate in a reaction that involved simply the replacement of the halogen. It may be seen from Table I that the three esters (5, 8 and 9) containing a bromine in the β-position are definitely the most reactive ones of the whole group. Even though these esters give mainly tertiary amines with piperidine their high reactivities indicate that this reaction product is not the result of a simple replacement reaction. A comparison of the amounts of tertiary amine formed in different reaction times (Table II) suggests that the actual course by which each of these esters forms the tertiary amine is through the loss of hydrogen bromide and the addition of piperidine to the resulting unsaturated ester. Thus, ethyl β-bromopropionate has reacted to approximately the same extent (97.5%, run 5) in fifteen minutes as it has in eight hours (run 6) but the amount of tertiary amine formed (column D) is greater after the longer reaction period. This increase in tertiary amine formation with time of reaction is more strikingly shown by ethyl β-bromoisobutyrate (runs 9 and 10) and ethyl β-bromobutyrate (runs 11 and 12). Such a conclusion as to the course of the reaction is further supported by the facts: (1) that under the same reaction conditions ethyl β-bromopropionate gave 66.5% reaction with N-methylpiperidine in fifteen minutes and (2) acrylic ester and piperidine gave a 95% yield of ethyl β-piperidinopropionate when heated together in petroleum ether solution for fifteen minutes at 90°.

From the data which are now available it may be safely concluded that organic bromides may undergo two distinctly different and, in some cases, simultaneously occurring reactions with piperidine, (a) the replacement of the halogen by the piperidino radical with the formation of a tertiary amine and (b) the elimination of hydrogen bromide with the formation of an unsaturated compound. With the exception of the β-bromo esters, the order of reactivity for reaction (a) is primary > secondary > tertiary, while for reaction (b) the order is reversed, tertiary > secondary > primary. With the primary and tertiary bromides one of these reactions is relatively so fast that the competing reaction is usually unimportant[8] and it is only in the case of the secondary bromides that both types of reactions appear to take place simultaneously to any appreciable extent.

If the true course of the reaction of β-bromo esters involves, as it now appears, the elimination of hydrogen bromide, some reasonable conclusions in regard to the mechanism of the reaction seem possible. Since the work of Conant and Kirner[7] shows that a carbethoxy group in the β-position to a chlorine atom does not greatly enhance its reactivity for replacement by iodine, it would seem necessary to ascribe the unusual reactivity of the β-bromo esters toward piperidine to the enhanced activity of the α-hydrogen caused by the adjacent carbethoxy group due to its electromeric or T effect as well as its inductive (I) effect. On this basis, then, the first step in the elimination reaction would be the removal of a proton from the α-carbon atom by the unshared electrons of the piperidine nitrogen, followed by the release of a bromide ion from the molecule, thus



The slightly lower reactivity of ethyl β-bromoisobutyrate (No. 8, Table I) may be attributable to the fact that this ester has only one-half the available α-hydrogens of the other β-bromo esters or possibly to the inductive (I) effect of the α-

(6) The only tertiary bromo ester studied was ethyl α-bromoisobutyrate. It shows a decidedly lower rate of reaction (Table I) than the other α-bromo esters and also forms a considerable amount of tertiary amine (Run 4, Table II). This tertiary amine, however, is the same ethyl β-piperidinoisobutyrate that is obtained from ethyl β-bromoisobutyrate and is undoubtedly formed from the α-bromo ester by the elimination of hydrogen bromide followed by the addition of piperidine to the resulting α-methylacrylic ester.

(7) Conant and Kirner, THIS JOURNAL, **46**, 232 (1924).

(8) For example, tertiary butyl bromide reacts to the extent of 92% in forty-eight hours at 150–155° but forms only 3% of the theoretical amount of tertiary amine (Ref. 1c).

methyl group.[9] Presumably, on the basis of this mechanism, the effectiveness of a reagent in bringing about this elimination reaction would be a function of its basicity and in this connection it should be noted that Segaller[10] found that the reagents which he studied stood in the following order, potassium hydroxide > sodium ethoxide > sodium phenoxide > sodium nitrophenoxide in their ability to form isobutylene from tertiary butyl iodide.

The mechanism by which the replacement of the halogen by the piperidino radical takes place is not so clear. It does not seem that the incipient ionization of the halogen is the rate controlling factor for this should be increased by the inductive (I) effect of the alkyl groups in the secondary and tertiary halides and hindered by both the I and T effect of the carbethoxy group (particularly when the bromine is on the α-carbon atom). It remains, therefore, to suggest that the rate-determining factor in this replacement reaction is the ability of the reagent to approach the carbon atom carrying the halogen. The concentration of electrons about this carbon by the inductive effect of the alkyl groups in secondary and tertiary bromides would make more difficult the approach and attachment of the unshared electron pair of the piperidine molecule while the withdrawal of electrons through the I and T effects of the carbethoxy group would facilitate the attachment of piperidine to the α-carbon atom in the case of ethyl bromoacetate. On the basis of such a mechanism the effects of the associated groups appear to explain the reactivities of the various bromides whose replacement reactions with piperidine have been studied.

(9) In this connection it should be noted that in a footnote to a paper by Noller and Dinsmore, THIS JOURNAL, **54**, 1032 (1932), it is stated that a referee suggested the removal of a proton by the base (in this case, pyridine) as the first step in the elimination of halogen acid from a halide and that tertiary halides lose halogen acid more readily than other types because of the larger number of hydrogens available for the reaction.

(10) Segaller, *J. Chem. Soc.*, **103**, 1421 (1913).

Summary

The rate and course of the reaction of thirteen different bromo esters with piperidine have been determined and from the results obtained mechanisms for the elimination of halogen acid and for the reaction involving replacement of the halogen by the piperidino radical have been suggested.

MADISON, WISCONSIN RECEIVED NOVEMBER 24, 1933

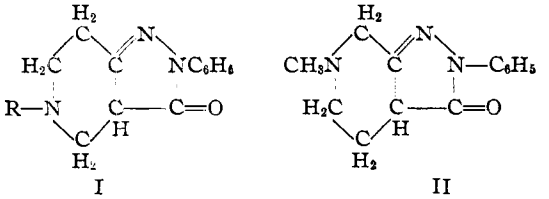
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Pyrazolones Derived from the Carbethoxypiperidones

BY S. M. ELIZABETH ENGLERT AND S. M. MCELVAIN

In previous publications[1] a variety of carbethoxypiperidones has been described. It seemed worth while to study the reaction of these substances with phenylhydrazine and to isolate, if possible, the various bicyclic pyrazolones that would be expected to result from such a condensation. The preparation of compounds of this type would not only extend the list of bicyclic pyrazolones to the heterocyclic field, but also would yield materials of possible pharmacological interest.

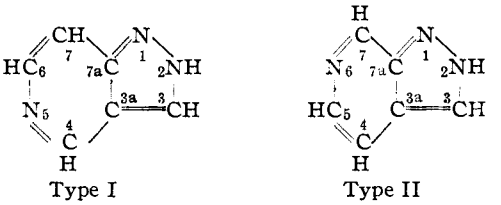
The present paper describes a series of 4,5,6,7-tetrahydro-2-phenyl-5-alkyl-2,1,5-pyrazolo-pyridin-3(3a)-ones[2] (I) derived from 1-alkyl-3-carbethoxy-4-piperidones,[1a] and also the isomeric 4,5,6,7-tetrahydro-2-phenyl-6-methyl-2,1,6-pyrazolopyridine-3(3a)-one (II) derived from 1-methyl-4-carbethoxy-3-piperidone.[1b]



I II

(1) (a) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926); (b) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(2) The nomenclature for this type of bicyclic structure was suggested by Dr. Leonard T. Capell, associate editor of *Chemical Abstracts*. Compounds I and II are considered as derivatives of pyrazolopyridine and the ring system is numbered thus



Type I Type II

The points of fusion of the pyridine and pyrazoline rings are indicated by the numbers of the three nitrogen atoms in the bicyclic system. Thus, giving the number of the nitrogen which carries the hydrogen first, type I is a 2,1,5-pyrazolopyridine and type II a 2,1,6-pyrazolopyridine. The hexahydro nature of I and II (piperidine derivatives) is indicated by the 4,5,6,7-tetrahydro prefix and the " 3(3a)-one" part of the name, since in order to form the keto group in position 3 another hydrogen must be added and is shown by the 3a in parentheses.