lized, 157–158°. Found: C, 19.49; H, 4.94; N, 13.33; S, 10.39. L-crude, m.p. 148–150°; recrystallized, m.p. 155–157°. Found: C, 19.30; H, 4.70; N, 13.43; S, 10.32. High melting form D-crude, m.p. 177–179°; recrystallized, m.p. 183–185°. Found: C, 19.34; H, 5.00; N, 13.40; S, 10.58. L-crude, m.p. 176–179°; recrystallized, m.p. 184–186°. Found: C, 19.35; H, 4.80; N, 13.50; S, 10.45.

The optical rotations of the polymorphic forms of the L and D isomers are identical: D- $[\alpha]^{22}_{D}$ −12.5° (*c*, 5% 0.2 *M* HCl). Converted to the mercaptoguanidine by the addition of sodium hydroxide to pH 8.0, the rotation is $[\alpha]^{22}_{D}$ +7.50° (*c*, 2%, 0.4 *M* phosphate buffer pH 8.0). Correspondingly, the L isomer in acid gives a rotation of $[\alpha]^{22}_{D}$ +12.0° (*c*, 5% 0.2 *M* HCl), and as the mercaptoguanidine $[\alpha]^{22}_{D}$ −7.3° (*c*, 2% 0.4 *M* phosphate buffer pH 8.0).

D- and L-2-Guanidobutanethiol Flavianate.—D-2-Aminobutylisothiourea (1.1 g.) was dissolved in 5 ml. of water, and the pH brought to 8.0 by the addition of 3.4 ml. of sodium hydroxide. The addition of 3.5 ml. of 1 *M* flavianic acid precipitated a yellow gum, which crystallized upon scratching with a glass rod. The product was filtered, dried (1.3 g.), and recrystallized from 10 ml. of hot 50% ethanol; 1.1 g., m.p. sinter 115°; melts 128–30°. The L-flavianate was prepared in a similar fashion, and had the same melting point.

Anal. Calcd. for $C_{15}H_{19}N_5O_8S_2$ (461.48); C, 39.04; H, 4.15; N, 15.18; S, 13.89. Found: D-, C, 39.16; H, 3.97; N, 15.09; S, 13.61. L-, C, 38.90; H, 4.08; N, 15.06; S, 13.70. D-, $[\alpha]^{22}_{D}$ +6.6°; L-, −6.2° (*c*, 0.5% water).

Bis-DL-, D-, and L-(2-Guanidobutyl) Disulfide Dihydrobromide.—A solution of DL-2-aminobutylisothiourea dihydrobromide, 15.5 g. in 50 ml. of water, was immediately converted to 2-guanidobutanethiol by the addition of 50 ml. of 1 *N* sodium hydroxide, the pH adjusted to 9.0, a few milligrams of cupric chloride added and oxygen bubbled through until the nitroprusside test was negative (*ca.* 3–4 hr.). The solution was acidified to pH 4 with hydrobromic acid, evaporated to dryness *in vacuo*, and the solid extracted with absolute ethanol. Ether was added to the ethanol extract to turbidity, and the mixture allowed to crystallize at −5°. Yield: 8.2 g. (72%), m.p. 173–175°. Recrystallization from absolute ethanol-acetone raised the melting point to 180–182°. The D and L disulfides were obtained in a similar manner.

Anal. Calcd. for $C_{10}H_{26}N_6S_2Br_2$ (454.34): C, 26.43; H, 5.77; N, 18.50; S, 14.11. Found: DL-, C, 26.22; H, 5.74; N, 18.23; S, 13.95. D-, M.p. 183–184°, $[\alpha]^{22}_{D}$ −198°. Found: C, 26.66; H, 5.75; N, 18.21; S, 14.24. L-, M.p. 183–185°, $[\alpha]^{22}_{D}$ +200°. Found: C, 26.71; H, 5.90; N, 18.30; S, 13.90.

DL-, D-, **and** L-**2-Amino-4-ethylthiazoline Hydrobromide.**—The thiazolines were prepared by the method of Gabriel.[15] For the corresponding aminoalkyl bromide hydrobromide, 11 g. (0.05 mole) was mixed with 5.0 g. (0.05 mole) potassium thiocyanate and 25 ml. water in an evaporating dish and heated on the steam bath overnight. The residue was extracted with 100 ml. hot isopropanol, potassium bromide filtered off and the filtrate evaporated *in vacuo* to dryness. The crystalline product was removed with ethyl acetate, filtered, and dried. Yield: 8 g. (75%), DL-, m.p. 102–104°.

Anal. Calcd. for $C_5H_{11}N_2S\ Br$ (211.14): C, 28.44; H, 5.25; N, 13.27; S, 15.19. Found: C, 28.46; H, 5.06; N, 13.12; S, 15.39. D-, M.p. 121–22°, $[\alpha]^{21}_{D}$ +26° (*c*, 2% H_2O). L-, M.p. 121–122.5°, $[\alpha]^{21}_{D}$ −25.8° (*c*, 2%, H_2O). Found: C, 28.54; H, 5.19; N, 13.10; S, 15.35.

The DL thiazoline yielded a flavianic acid salt identical with that obtained by Khym, *et al.*,[4] from the rearrangement of the isothiourea in acid solution.

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[15] S. Gabriel, *Ber.*, **22**, 1141 (1889); G. W. Raiziss and W. C. Le Roy, *J. Am. Chem. Soc.*, **63**, 3124 (1941); A. Schoberl, R. Hamm, and M. Kawohl, *Chem. Ber.*, **84**, 571 (1951).

Aroyldiazoacetic Esters. II. Synthesis with Anhydrous Methyl Diazoacetate. Hydrolysis of Aroyl Halides in 96% Methyl Diazoacetate[1-4]

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Preparation of aroyldiazoacetic esters by direct interaction of aroyl halides and methyl diazoacetate (I) is a general procedure if I is anhydrous. There is described a procedure for drying I azeotropically with *n*-pentane, which permits quantitative estimation of water present. Interaction of aroyl chlorides with 96% methyl diazoacetate resulted in hydrolysis products, either alone or together with the aroyldiazoacetic ester. A bimolecular hydrolysis of aroyl chlorides in 96% methyl diazoacetate is proposed. A new mechanism for aroyldiazoacetic ester formation is postulated.

The reaction of acyl halides with diazoacetic esters to give acyldiazoacetic esters is well known. However, benzoyl bromide appears to be the sole example of an *aroyl* halide undergoing this reaction.[6] The heterocycles, furoyl bromide and chloride, react with methyl diazoacetate (I) to give methyl (α-furoyl)diazoacetate in 80% and unstated yields, respectively.[7] Our attempts to extend this reaction led to carboxylic anhydrides and an O-aroylglycollate as products.[8] The present paper describes a procedure for drying I azeotropically, reaction of anhydrous I with several aroyl halides to give crystalline aroyldiazoacetic esters, and reaction of I containing known amounts of water with aroyl halides.

The products obtained from interaction of methyl diazoacetate with aroyl chlorides in our previous study indicated water to be present in I. In the preparation of I by the procedure of Womack and Nelson,[9] the effect of certain operations on the water content of the product diazoacetic ester had not been previously determined. We report that I can be dried azeotropically with *n*-pentane, and the azeotrope collected in a modification of the distilling head used in the Dean–Stark procedure[10] to afford a direct measure of water present. The modification substitutes a capillary tube of known cross section for the usual graduated test tube of the

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(1) Paper I: J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(2) From the Ph.D. thesis of Charles H. Hayes, University of Nebraska, 1959.

(3) Presented before the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(4) Partial support of this work by the Research Corporation of New York and by The University of Nebraska Research Council is gratefully acknowledged.

(5) Dow Chemical Company Fellow, 1955–1956.

(6) H. Staudinger, J. Becker, and H. Hirzel, *Ber.*, **49**, 1978 (1916).

(7) T. Reichstein and H. J. Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).

(8) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **23**, 403 (1958). This paper contains references to extensive review articles on aliphatic diazo chemistry.

(9) E. B. Womack and A. B. Nelson, *Org. Syn.*, **24**, 56 (1944).

(10) The unmodified Dean–Stark distilling receiver is available from E. H. Sargent & Co., and is listed as a water trap for determination of water in petroleum products in accordance with A.S.T.M. method D-95.

TABLE I

REACTION CONDITIONS[a] AND YIELD DATA

$$\mathrm{RCOX} + \underset{\mathrm{I}}{2\mathrm{CHN_2CO_2CH_3}} \longrightarrow \mathrm{RCOCN_2CO_2CH_3} + \mathrm{CH_2XCO_2CH_3} + \mathrm{N_2}$$

RCOX	Ordinal	Reaction period, days	Product isolation method[b]	Solvent for crystallization[c]	Ratio: moles I/-moles RCOX	Yield, %
Benzoyl chloride	II	12	A	M–P	2.2	62.5
m-Bromobenzoyl bromide	III	8[d]	B	M–P	2.2	68.5
m-Bromobenzoyl bromide	III	2.5 hr.	..	...	2.0	0 (Explosion)
m-Bromobenzoyl chloride	IV	37	C	M–P	2.2	69.7
3,5-Dinitrobenzoyl chloride	V	3	A	M–P	2.2	90.1
o-Iodobenzoyl chloride	VI	16	C	M–P	2.2	53.2
p-Mesyloxybenzoyl chloride	VII	3	A	M–P	2.2	73.2
o-Nitrobenzoyl chloride	VIII	50[d]	B	M–P	3.0	61.7
m-Nitrobenzoyl chloride	IX	22	A	M–P	2.2	72.5
p-Nitrobenzoyl chloride	X	2	A	M	2.2	91.4
o-Chlorobenzoyl chloride	XI	47	D	...	2.2	(Oil)
m-Chlorobenzoyl chloride	XII	33	C	M–P	2.2	64.0
p-Chlorobenzoyl chloride	XIII	29	A	M–P	2.2	57.3
o-Methoxybenzoyl chloride	XIV	18	D	...	2.2	(Oil)
m-Methoxybenzoyl chloride	XV	38	D	...	2.2	(Oil)
Furoyl chloride	XVIII	18[d]	A	ET	2.2	51.2
Furoyl chloride	XVIII	14[e]	A	M	2.1	52.4
5-Nitrofuroyl chloride	XIX	4	A	M–P	2.2	80.6
Hydrocinnamoyl chloride	XX	35	E	...	2.7	(Oil)
Phenoxyacetyl chloride	XXI	20 hr.[f]	A	B–SK and M–P	2.1	72.4

[a] Anhydrous I employed except where otherwise noted. [b] A: Product crystallized from reaction mixture; reaction vessel scraped with stirring rod if necessary. B: Product isolated by nucleation, or by scratching of reaction vessel, and strong cooling. C: Small portion of reaction mixture permitted to evaporate in air; crystalline residue used to seed reaction mixture. D: Reaction mixture was steam distilled at reduced pressure; solvent removal from dry ethereal solution of residue gave oily product. E: As in D, except that 2 g. of $Ba(OH)_2$ present during steam distillation, and solvent removal from dry benzene solution. [c] M = methanol; P = petroleum ether, b.p. 60–69°; ET = ether; B = benzene; SK = Skellysolve C (petroleum ether, b.p. 88–98°). [d] I contained trace of water. [e] I contained 2.1% of water. [f] I contained 4.0% of water.

TABLE II

AROYLDIAZOACETIC ESTERS[a]: PROPERTIES AND ANALYTICAL DATA

Aroyldiazoacetic ester	Acid halide for synthesis	M.p., °C.	Infrared absorption bands,[b] cm.$^{-1}$			Analysis, % N	
			CN_2	Ester CO	Keto CO	Calcd.	Found
XXII	II	84.5–85.5	2162	1716	1616	...	...
XXIII	III or IV	65-67	2140	1724	1622	9.90	9.76
XXIV	V	126.5 dec.	2156	1710	1640	19.05	18.73
XXV	VI	73.5–75	2148	1709	1638	8.94	8.58
XXVI	VII	105–106 dec.	2160	1721	1623	9.39	9.02
XXVII	VIII	90–92	2156	1712	1634	16.86	16.89
XXVIII	IX	87.5–89	2156	1726[c]	1625	16.86	17.02
XXIX	X	91.5–92.5	2160	1726	1632	16.86	17.30
XXX	XII	64.5–66.5	2156	1726[d]	1624	11.74	11.27
XXXI	XIII	105.5-107.5	2144	1717	1623	11.74	11.17
XXXII	XVIII	111-112	2140	1732	1623	14.28	14.47
XXXIII	XIX	97–99	2134	1739	1629	17.14	17.39
XXIV[e]	XXI	105.5–106.5	2148	1706	1668	11.96	11.92
XXXV[f]	III	56-58	2156	1727[g]	1622	9.42	8.86

[a] Methyl ester, unless otherwise indicated. [b] Of Nujol mull. [c] Shoulder on strong band at 1695 cm.$^{-1}$. [d] Shoulder on strong band at 1688 cm.$^{-1}$. [e] Acyldiazoacetic ester. [f] Ethyl ester. [g] Shoulder on strong band at 1687 cm.$^{-1}$.

distilling head. Distillation of I itself is not necessary. Freshly prepared methyl diazoacetate and the reagent which has been stored in a refrigerator for *ca.* six months contain 2.1% and 4.0% water, respectively. In contrast, ethyl diazoacetate which had been stored for one to two years under the same conditions possessed only a trace of water. When I was prepared by the method of Hammond,[11] I contained only a trace of water.

Data pertaining to the reactions of I with acid halides are reported in Table I. Acid halide for synthesis, properties, and analytical data for product aroyldiazoacetic esters are outlined in Table II. In Table II, the structure of the aroyldiazoacetic ester is apparent from that of the acid halide for synthesis. Product distributions from, and reaction conditions for, interaction of aroyl halides with I containing up to 4.0% water are given in Table III.

The combined data of Tables I and II establish the general nature of the reaction of I with aroyl chlorides to give aroyldiazoacetic esters, with the important provision that I must be anhydrous. The reaction conditions employed are not considered optimum, however, with the exception of those for preparation of aroyl-

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(11) J. A. Hammond, U. S. Patents 2,691,649 and 2,691,650; *Chem. Abstr.*, **49**, 11690 (1955).

TABLE III

PRODUCTS FROM INTERACTION OF AROYL HALIDES WITH METHYL DIAZOACETATE (I) CONTAINING 4.0%[a] WATER

ArCOX	Ratio: moles I/-moles RCOX	Reaction period, days	Product distribution Yield, % ArCOCN$_2$-CO$_2$CH$_3$	ArCO$_2$H	(ArCO)$_2$O
III	2.0	14[b]	49.4	...	...
IV	3.0	50[c]	...	1.1	...
VII	2.1	16 (hr.)	6.2	...	34.5
IX	2.1	3	10.5	...	42.5
X	2.1	3	40.0	...	33.6
XI	2.1	2	...	...	33.3
XII	3.0	161[c]	8.5	2.1	...
XIII	2.8	3	10.4	...	39.0
XIII	2.1	2	...	0.8	27.8
XIV	2.1	0.5	...	...	43.8
XV	3.0	77[c]	...	5.75	...
XVI	2.1	8	...	6.0	32.0
XVII	3.0	160[c]	...	19.4	12.3
XVIII	2.9	7	26.7	...	...

[a] Unless otherwise indicated. [b] In this experiment, I contained approximately 2% water. [c] In this experiment, I contained a trace of water initially.

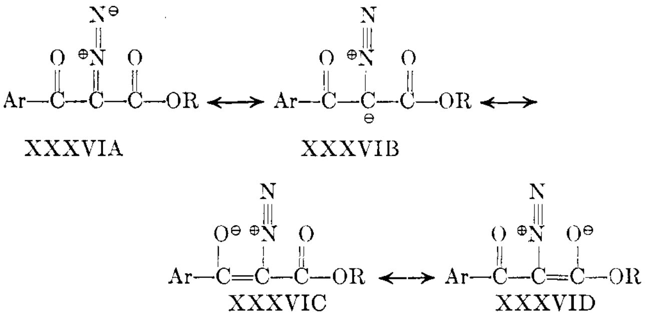
diazoacetic esters XXIV and XXIX which gave yields of over 90%. In the majority of cases, the reaction product crystallized from the reaction mixture directly, but also very slowly in certain instances. The synthesis of XXII has been previously reported, but not from benzoyl chloride. Acid chlorides XI, XIV, and XV gave oily reaction products, which resisted all attempts at purification. However, these products gave positive tests with bromine in acetic acid (sequel), and very probably were the aroyldiazoacetic esters. Anisoyl chloride (XVI) and *p*-toluyl chloride (XVII) were the least reactive of the acid chlorides studied. At least 61% of XVI was present after 18 days, and the only products isolated from XVII and I were toluic acid and its anhydride. These latter two products apparently resulted from a reaction with water, slowly introduced into I during the long reaction period (82 days at −24°, after 78 days at room temperature). The heterocyclic acid derivatives, furoyl chloride (XVIII) and its 5-nitro derivative (XIX), reacted satisfactorily with I. The aliphatic acid chloride XXI gave a satisfactory yield of methyl (phenoxyacetyl)diazoacetate, even when I contained 4.0% water. This property is in marked contrast to that of most aroyl chlorides. With anhydrous I, hydrocinnamoyl chloride (XX) gave as reaction product an orange oil, which gave a positive test with bromine in acetic acid.

Certain properties of the crystalline aroyldiazoacetic esters obtained in this study are given in Table II. In addition, all such substances gave a moderate evolution of nitrogen with 1% bromine in acetic acid. This test is based on the known reaction of the aliphatic diazo group with halogen,[12] and presumably proceeds as in equation 1. Although I also undergoes the test, its

$$\text{Ar—COCN}_2\text{COOCH}_3 + \text{Br}_2 \longrightarrow \text{Ar—COCBr}_2\text{COOCH}_3 + \text{N}_2 \quad (1)$$

reaction is more violent than that with the aroyldiazoacetic esters. The test with bromine is of added significance because of the acid-stability of the diazo function in acyl- and aroyldiazoacetic esters. This acid-stability was so striking that, at one time, an oxadiazole structure was advocated for such molecules.[13] Subsequent infrared[1] and chemical[14] studies do not permit such a view today, however.

Comparison of infrared spectra of aroyldiazoacetic esters (Table II) with those of diazo ketones[15] indicates that the diazo group in aroyldiazoacetic esters absorbs somewhat higher frequency radiation. Possibly this property is due to enhanced triple bond character in the diazo function of diazoacetic ester derivatives (XXXVI B, C, and D).


XXXVIA XXXVIB XXXVIC XXXVID

The data of Table III give the product distribution resulting from interaction of aroyl halides with I containing from a trace to as much as 4.0% water, and afford convincing evidence for the importance of anhydrous methyl diazoacetate in synthesis of aroyldiazoacetic methyl esters. Of particular interest are reactions of acid chlorides IV, VII, IX, X, XII, XIII, and XVIII (Table III), which gave moderate to excellent yields of aroyldiazoacetic esters with anhydrous I (Table I).

The general course of the reaction of aroyl chlorides with water and I is clear. Part of the aroyl chloride is first hydrolyzed to the carboxylic acid, which then reacts with unreacted acid chloride to give the anhydride. In both steps, I acts as a base. The proposed sequence is outlined in equations 2–5.

$$\text{ArCOCl} + \text{H}_2\text{O} \longrightarrow \text{ArCOOH} + \text{HCl} \quad (2)$$

$$\text{CHN}_2\text{COOCH}_3 + \text{HCl} \longrightarrow \text{CH}_2\text{ClCOOCH}_3 + \text{N}_2 \quad (3)$$

$$\text{ArCOOH} + \text{ArCOCl} \longrightarrow (\text{ArCO})_2\text{O} + \text{HCl} \quad (4)$$

$$\text{CHN}_2\text{COOCH}_3 + \text{HCl} \longrightarrow \text{CH}_2\text{ClCOOCH}_3 + \text{N}_2 \quad (5)$$

Presumably the over-all reaction for anhydride formation is that given in equation 6.

$$2\text{ArCOCl} + 2\text{CHN}_2\text{COOCH}_3 + \text{H}_2\text{O} \longrightarrow (\text{ArCO})_2\text{O} + 2\text{CH}_2\text{ClCOOCH}_3 + 2\text{N}_2 \quad (6)$$

One example of ester formation in I was observed, namely, reaction of benzoyl chloride with excess methanol to give methyl benzoate (equation 7).

$$\text{C}_6\text{H}_5\text{COCl} + \text{CH}_3\text{OH} + \text{CHN}_2\text{COOCH}_3 \longrightarrow \text{C}_6\text{H}_5\text{COOCH}_3 + \text{CH}_2\text{ClCOOCH}_3 + \text{N}_2 \quad (7)$$

Data of theoretical interest pertain to whether or not hydrolysis of aroyl bromides and chlorides in methyl diazoacetate containing water occurs. Benzoyl bromide and *m*-bromobenzoyl bromide react with I containing 4.0% and 2% of water respectively to give the aroyldiazoacetic ester in 78 and 49% yields. Furoyl bromide gives an 80% yield of the furoyldiazoacetic

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(12) L. Wolff, *Ann.*, **394**, 23 (1912); ref. 6.

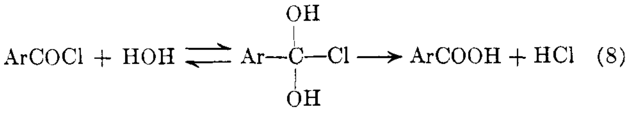
(13) L. Wolff, *ibid.*, **325**, 129 (1902); L. Wolff and A. A. Hall, *Ber.*, **36**, 3612 (1903).

(14) H. Staudinger, *ibid.*, **49**, 1884 (1916).

(15) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957). This work contains the spectrum of one acyldiazo ester.

ester with I of unstated water content.[16] In this study, the carboxylic anhydride was not detected as a reaction product from aroyl bromides and I, even when I contained water. Hydrolysis of benzoyl bromide can be effected with water and I, but the 25% water present probably would permit an S_N1 type hydrolysis (sequel), and the product was benzoic acid. We conclude that aroyl bromides are not readily hydrolyzed in methyl diazoacetate containing small amounts of water (under 5%). In contrast, the common reaction path of aroyl chlorides with 96% methyl diazoacetate leads to a mixture of the aroyldiazoacetic ester and hydrolysis product, or hydrolysis product exclusively. Under consistent conditions, of 2.1 moles of I per mole of acid chloride and 4.0% water in the methyl diazoacetate, VII, IX, and X formed both aroyldiazoacetic ester and anhydride, while XI, XIII, and XIV (Table III) gave no aroyldiazoacetic ester, with the anhydride being the main product. We conclude that aroyl chlorides are hydrolyzed rather readily in 96% methyl diazoacetate. Apparently the acyl chloride (XXI) (Table I) resembles aroyl bromides in its reaction with 96% methyl diazoacetate.

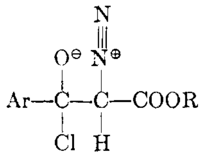
Two extreme mechanisms for acid halide hydrolysis have been recognized.[17] First (equation 8), hydrolysis is effected *via* a bimolecular reaction, probably involving addition of water to the carbonyl group to give the intermediate XXXVI. Second (equation 9), an S_N1 type ionization occurs without formation of a geminal diol intermediate. Kinetic hydrolysis studies by other workers[17] indicate that many acid chlorides can undergo hydrolysis by either mechanism, *depending on the concentration of water in the hydrolysis medium.* Low concentrations of water favor the path in equation 8, high concentrations that in 9. The hydrolysis media in this study contained from a trace to as much as 4% water, low concentrations, and we postulate that most of the aroyl chloride hydrolyses (Table III) occur *via* the path of equation 8. The S_N1 mechanism (equation 9) very probably is important in the hydrolysis of benzoyl bromide with 25% water present.



$$\text{ArCOCl} + \text{HOH} \rightleftharpoons \text{Ar}-\overset{\text{OH}}{\underset{\text{OH}}{\text{C}}}-\text{Cl} \longrightarrow \text{ArCOOH} + \text{HCl} \quad (8)$$

XXXVI

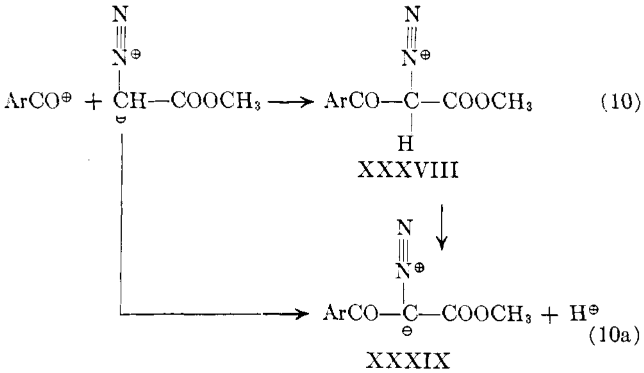
$$\text{ArCOX} \rightleftharpoons \text{X}^{\ominus} + \text{ArCO}^{\oplus} \xrightarrow{\text{HOH}} \text{ArCOOH} + \text{H}^{\oplus} \quad (9)$$



XXXVII

The dichotomy of hydrolysis mechanisms for acid halides, and the importance of medium in determining mechanism, indicate the possibility of two extreme mechanisms for formation of aroyldiazoacetic esters from acid halides. The first, the Eistert mechanism,[18] is a bimolecular one in which the intermediate XXXVII is formed by addition of the diazoacetic ester molecule to the carbonyl group of the acid chloride. In the second, not known to be previously postulated, ionization of the aroyl halide would occur as in equation 9; and the carbonium ion formed would react with methyl diazoacetate (I) to give the C-aroyldiazonium ion XXXVIII (equation 10). Interaction of XXXVIII, possibly associated with bromide ion as in XL, with the base (I) would give the product diazonium ion (equation 11). Although less likely, a displacement (equation 10a) is conceivable. The exact species involved in proton transfer to I is not known, although a formal ionization of XXXVIII to XXXIX and the "bare proton" is indicated for convenience. We term this second mechanism the aroyldiazonium ion mechanism for aroyldiazoacetic ester formation.

The Eistert mechanism[18] is quite adequate if acid halide hydrolysis is impossible and ionization cannot occur in the reaction medium, as in reaction of aroyl halides with either diazomethane or diazoacetic ester in anhydrous ether solution. In general, the aroyldiazonium ion mechanism would be important if the medium is sufficiently polar to facilitate ionization of readily ionizable acid halides. In the present work, the reaction medium, initially either anhydrous liquid I or a homogeneous mixture of I with small quantities of water, very probably would support ionization. A rough correlation between hydrolysis mechanism and aryoldiazoacetic ester formation mechanism is possible. Acid halides undergoing hydrolysis by the path of equation 9 would be expected to form aroyldiazoacetic esters by the aroyldiazonium ion mechanism, *providing the polarity of the medium would permit ionization of the acid halide.* Acid halides undergoing hydrolysis by the path of equation 8 would form aroyldiazoacetic esters by the Eistert mechanism, assuming a suitable medium. Benzoyl bromide, *m*-bromobenzoyl bromide, and phenoxyacetyl chloride are probable specific examples of acid halides which react with 96% or 98% I to form the aroyldiazoacetic (or acyldiazoacetic) ester by the aroyldiazonium (acyldiazonium) ion mechanism.



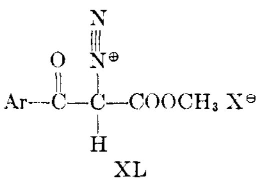
(10)

XXXVIII

(10a)

XXXIX

$$\text{H}^{\oplus} + \text{CHN}_2\text{COOCH}_3 \longrightarrow \text{N}{\equiv}\overset{\oplus}{\text{N}}-\text{CH}_2-\text{COOCH}_3 \quad (11)$$



XL

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[16] Presumably the methyl diazoacetate used would have contained at least traces of water, since no drying step was described (ref. 7).

[17] M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 225-227; E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 501 (1956), and preceding papers; H. K. Hall, Jr., *J. Am. Chem. Soc.*, **77**, 5993 (1955).

[18] B. Eistert, *Ber.*, **68**, 208 (1935).

Experimental

Melting points are uncorrected unless stated otherwise. Temperatures of −4° and −24° represent average temperatures of the middle of main box and freezing compartment respectively of the refrigerator used. Unless stated otherwise, yields were determined from crude product after it had stood over phosphorus pentoxide in a vacuum desiccator at room temperature and 15–20 mm. for a minimum of 12 hr. All reactions were carried out at room temperature unless otherwise noted. EK designates an Eastman Kodak chemical of White Label purity.[19] Infrared spectra were determined as Nujol mulls unless otherwise noted, on a Perkin–Elmer Model 21 spectrophotometer (sodium chloride optics). Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Methyl Diazoacetate.—This substance was prepared from glycine methyl ester hydrochloride by the method of Womack and Nelson,[9] and by the procedure of Hammond.[11]

Azeotropic Purification of Methyl Diazoacetate.—The apparatus used consisted of a round-bottom flask of suitable size, an efficient water-cooled condenser, and a modification of the Dean-Stark water determination apparatus.[10] A capillary tube of known cross section, uniform bore, and approximately 15 cm. in length, with a stopcock at the lower end, was substituted for the graduated test tube of the latter apparatus. Heat was supplied carefully by means of a heating mantle. The azeotrope involved was *n*-pentane–water.

A sample of methyl diazoacetate (32.7 g.), prepared by Womack and Nelson's procedure, that had been stored in a brown, glass-stoppered bottle at −4° for approximately 6 months was heated with 50 ml. of *n*-pentane under reflux until no further condensation of water could be observed in the condenser; water content, 1.30 g. (4.0%). A freshly prepared sample of methyl diazoacetate (51.7 g.) was heated with *n*-pentane under reflux as before to give dry methyl diazoacetate and water (1.10 g., 2.1%).

Preparation of Aroyldiazoacetic Esters. Procedure A.[20]—Recrystallized 3,5-dinitrobenzoyl chloride, m.p. 69–71° (15.0 g., 0.065 mole) was added in portions to dry methyl diazoacetate (14.3 g., 0.143 mole) over a 45-min. period with stirring in a three-neck round-bottom flask equipped with thermometer, efficient stirrer, and a device consisting of a 19/38 ground glass joint and a 50-ml. erlenmeyer flask joined by a short section of large rubber tubing. The acid chloride was added through the latter device. The system was isolated from atmospheric moisture by a calcium chloride drying tube. Nitrogen was evolved rapidly from the initial addition of acid chloride; stirring was continued for 1 hr. after completion of the addition, with periodic strong cooling. The reaction mixture was allowed to stand in ice–water for 1 hr. without stirring, then at room temperature for 72 hr.; the entire reaction mixture had set to a semisolid mass. The crude, crystalline, yellow methyl (3,5-dinitrobenzoyl)diazoacetate (XXIV; Table II) was collected by filtration and dried. Two additional crops of crude product were combined with the first; total yield, 17.20 g. (90.1%), m.p. 90–120° dec. Recrystallization from methanol–petroleum ether (b.p. 60–69°) gave analytically pure material, m.p. 126.5°.

Procedure B.[20]—Freshly distilled *m*-bromobenzoyl bromide (14.6 g., 0.055 mole) was added dropwise to methyl diazoacetate (12.2 g., 0.122 mole) (cooled in an ice–water bath) in a three-neck flask equipped with dropping funnel, thermometer, and efficient stirrer. The system was protected from atmospheric moisture. The addition required 50 min. Initially, nitrogen was evolved rapidly. The reaction mixture stood undisturbed in an ice–water bath for 2 hr. It then was cooled intermittently until the reaction no longer became vigorous at room temperature, and was allowed to stand for 8 days. The yellow solution was seeded with authentic methyl (*m*-bromobenzoyl)diazoacetate; after standing overnight at −24°, the entire mixture had set to a semisolid mass. After standing 8 more days at −24°, the crude methyl (*m*-bromobenzoyl)diazoacetate (XXIII; Table II) (3 crops) was collected and dried.

Procedure C.[20]—Freshly prepared *m*-chlorobenzoyl chloride (b.p. 104° at 12 mm.) was added dropwise to dry methyl diazoacetate (15.6 g., 0.0156 mole) in apparatus as in procedure B. The addition to the stirred mixture required 10 min. Nitrogen was evolved at a moderate rate initially. Stirring was continued 15 min. after completion of the addition, and the resulting mixture stood for 33 days. A small portion of the yellow solution was allowed to evaporate in air. The crystalline residue was used to seed the solution, which stood overnight at −4°. There occurred crystallization of methyl (*m*-chlorobenzoyl)diazoacetate (XXX; Table II), which was collected and dried.

Procedure D.[20]—Freshly prepared *m*-methoxybenzoyl chloride, b.p. 96.5–98° at 2.5 mm., was added dropwise to dry methyl diazoacetate over a 10-min. period with stirring. Equipment was as in procedure B. Nitrogen was evolved at a moderate rate after an induction period of several minutes; stirring was continued 15 min. after completion of the addition. The reaction mixture stood for 38 days. The entire solution was subjected to steam distillation at reduced pressure.[21] Evaporation of the dry yellow ethereal extract of the residue gave 16.48 g. (96.6%) of a yellow oil, which gave a positive bromine in acetic acid test (sequel). Attempted crystallization of the oily product from methanol (charcoal) was unsuccessful, as was attempted distillation at reduced pressure. Repeated attempts to purify this material chromatographically on alumina did not lead to a demonstrably pure product.

Bromine in Acetic Acid Test.—A 1% by volume solution of bromine in glacial acetic acid was used as a reagent for determining presence of the diazo group. The procedure involved adding a portion of a possible diazo compound, about the size of a small pea, to approximately 1 cc. of the reagent. A positive test consisted of an immediate evolution of nitrogen and partial decoloration of the acetic acid solution.

Attempted Preparation of Methyl Anisoyldiazoacetate. Isolation of Anisic Acid.—EK anisoyl chloride (12.4 g., 0.073 mole) was added dropwise to dry methyl diazoacetate (16.0 g., 0.160 mole) over a period of 10 min. with stirring. Apparatus was as in procedure B. Initially nitrogen was evolved slowly. Stirring was continued for 15 min. after completion of the addition. The reaction mixture was allowed to stand for 16 days; however, no crystallization of product had occurred. All attempts to induce crystallization failed. The entire solution was subjected to vacuum steam distillation,[21] during which a vigorous reaction occurred. On completing the distillation, the crystalline solid present was collected, dried, and recrystallized from methanol–petroleum ether (b.p. 60–69°) to a m.p. of 182–185°; yield, 6.76 g. (61.0%), lit.,[22] m.p. 184.2°. Mixture melting point with authentic anisic acid showed no depression. Bromine in acetic acid test was negative.

Interaction of Acid Halides with 96% Methyl Diazoacetate. *o*-Chlorobenzoyl Chloride.—EK *o*-chlorobenzoyl chloride (3.98 g., 0.023 mole) was added dropwise to 96% methyl diazoacetate (5.00 g., 0.048 mole of methyl diazoacetate) over a period of 1 hr. Nitrogen was evolved at a moderate rate initially. After 48 hr., crystallization of product had not occurred. All attempts to induce crystallization failed. The yellow solution was dissolved in benzene–petroleum ether (b.p. 88–98°), cooled in an ice-water bath, and the sides of the reaction vessel scratched to cause formation of a crystalline material which was collected and dried; m.p. 77–125° dec. This product gave a positive bromine in acetic acid test. The crude product was recrystallized from methanol–petroleum ether (b.p. 60–69°); yield, 1.13 g. (33.3%), m.p. and mixture m.p. with authentic *o*-chlorobenzoic anhydride, 78–79.5° (lit.,[23] m.p. 78–79°). Bromine in acetic acid test was negative. Filtrate evaporation from isolation of *o*-chlorobenzoic anhydride gave a dark brown, intractable oil.

Reaction of Acid Chlorides with Methyl Diazoacetate Containing a Trace of Water Initially. *p*-Toluoyl Chloride.—Methyl diazoacetate was prepared by method of Hammond.[11] *p*-Toluoyl chloride (b.p. 104° at 17 mm.) (11.02 g., 0.071 mole) was added to methyl diazoacetate (21.42 g., 0.214 mole) over a 1-hr. period. Nitrogen was evolved slowly after an induction period. The reaction mixture stood 78 days without crystallization. After 82 additional days, at −24°, there separated a solid, m.p. 95–168° dec. (fraction A). Four additional fractions were obtained by cooling appropriate filtrates to −24°:

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[19] Highest purity available from Distillation Products Industries, Division of Eastman Kodak Co.

[20] For additional substances prepared by this method, see Tables I and II.

[21] The apparatus used was essentially that described by L. Gattermann and H. Wieland, "Laboratory Methods of Organic Chemistry," MacMillan and Co., New York, N. Y., 1937, pp. 277–279.

[22] A. Oppenheim and S. Pfaff, *Ber.*, **8**, 893 (1875).

[23] R. Adams, W. V. Wirth, and H. E. French, *J. Am. Chem. Soc.*, **40**, 424 (1918).

B, m.p. 69–140° dec., C, m.p. 163–180°, D, m.p. 142–168°, and E, m.p. 70–80°. The fractions were combined: A, C, and D gave first combined product, fractions B and E the second combined product. The first combined product (*p*-toluic acid) was recrystallized repeatedly from methanol; yield 0.78 g. (19%), m.p. and mixture m.p. 179–181.5° (lit.,[24] m.p. 181°). The second combined product (*p*-toluic anhydride) was recrystallized repeatedly from methanol–petroleum ether (b.p. 60–69°); yield 1.12 g. (12.3%), m.p. and mixture m.p. 95–96.5° (lit.,[25] m.p. 95°).

Hydrolysis of Benzoyl Bromide in 75% Methyl Diazoacetate.—EK benzoyl bromide (15.8 g., 0.087 mole) was added dropwise over 25 min. to a stirred mixture consisting of 75% methyl diazoacetate (17.58 g., 0.176 mole), previously dried azeotropically, and 25% water (5.9 g., 0.33 mole) at −4°. The temperature of the heterogeneous reaction mixture, initially cooled in ice, rose to 18° by the end of the acid bromide addition. Nitrogen was evolved rapidly from the initial addition of acid bromide. After nitrogen evolution ceased, crystals of product began to form in the mixture. Cooling in ice for several hours caused further separation of crystalline material (fraction A), m.p. 111–120°. The filtrate consisted of an upper organic layer, fraction B, and a lower aqueous layer that was separated and distilled. After collecting 2–3 ml. of distillate, b.p. 124°, the residual liquid was cooled to room temperature. A substance, m.p. 70–121°, separated (fraction C). Fractions A and C were combined and recrystallized repeatedly from water to give benzoic acid, m.p. and mixture m.p. 121–122°; yield 6.21 g. (60.1%). Bromine in acetic acid test was negative. Fraction B was a colorless liquid with an ester-like odor; yield 7.68 g., b.p. 215°. Bromine in acetic acid test was negative. This fraction was not identified.

Formation of Methyl Benzoate from Benzoyl Chloride and Methanol in Methyl Diazoacetate.—Benzoyl chloride (4.64 g., 0.033 mole) was added dropwise over 30 min. to a solution of methanol (3.96 g., 0.124 mole) in methyl diazoacetate (10.0 g., 0.100 mole), previously dried azeotropically. Nitrogen was evolved rapidly from the initial addition of acid chloride. After standing for 134 days, the reaction mixture was pale yellow and completely homogeneous. Distillation of the entire reaction mixture gave three fractions: (1) yield 4.44 g., b.p. 127.5–135°; (2) yield 1.51 g., b.p. 93–187°; (3) yield 2.13 g., b.p. 189.5–191°. Redistillation of fraction 1 gave a colorless distillate with an ester-like odor, product A; yield 2.25 g., b.p. 130–132°. Fraction 2 was added to residue from redistillation of fraction 1 and distilled to give more of product A; yield 0.84 g., b.p. 131–135°. Fraction 3 was added to residue from redistillation of fraction 2 and distilled to give a colorless distillate with an ester-like odor, product B; yield 2.84 g., b.p. 190–195°.

Product A was identified as methyl chloroacetate; total yield 3.09 g. (86.4%), n^{25}_D 1.4126 and d^{20}_4 1.184; lit. b.p. 130°,[26] n^{20}_D 1.42207[27] and d^{15} 1.22.[28] Product B was identified as methyl benzoate; yield 2.84 g. (63.3%), n^{25}_D 1.5118 and d^{20}_4 1.090; lit.,[29] b.p. 199.6°, n^{16}_D 1.51810 and d^{20}_4 1.088. A 0.81-g. quantity of product B was hydrolyzed in 5% sodium hydroxide to give 0.45 g. of benzoic acid, identified by melting point and mixture melting point.

Hydrolytic Cleavage of Methyl Benzoyldiazoacetate.—Methyl benzoyldiazoacetate (0.50 g., 0.0025 mole) was added in one portion to 10 ml. of 5% sodium hydroxide and allowed to stand undisturbed at room temperature for 24 hr. The reaction mixture was a clear yellow solution which evolved nitrogen slowly. Concentrated hydrochloric acid was added dropwise to the mixture, cooled in an ice–water bath, until slightly acid to litmus. There separated a colorless, crystalline solid (benzoic acid), m.p. 122.5–125°, which was recrystallized from water; yield 0.28 g. (93.6%), m.p. and mixture m.p. 122–123°. Bromine in acetic acid test was negative.

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[24] G. Ciamician and P. Silber, *Ber.*, **45**, 40 (1912).

[25] P. Frankland and F. M. Wharton, *J. Chem. Soc.*, **75**, 344 (1899).

[26] L. Schreiner, *Ann.*, **197**, 8 (1879).

[27] A. Karvonen, *Ann. Acad. Sci. Fennicae, Ser. A.*, **10**, 19 (1916).

[28] L. Henry, *Ber.*, **6**, 742 (1873).

[29] "Handbook of Chemistry and Physics," C. D. Hodgman, ed. Chemical Rubber Publishing Co., 1960–1961, p. 848.

The Reaction of *cis*-2,6-Dibromo-4,4-dimethylcyclohexanone with Sodium Acetate in Acetic Acid, a New Elimination–Rearrangement Reaction

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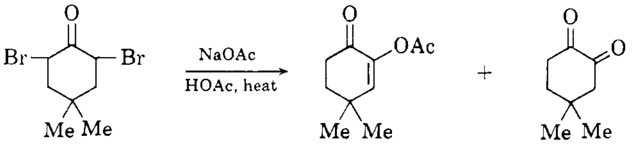
Reaction of *cis*-2,6-dibromo-4,4-dimethylcyclohexanone (I) with sodium acetate in acetic acid gives 2-acetoxy-5,5-dimethylcyclohex-2-enone (VIII) as the major product. Evidence is presented which suggests that VIII is formed by: (1) replacement of one bromine atom by an acetoxy group; (2) abstraction of the proton alpha to the acetoxy group; (3) intramolecular rearrangement of the acetoxy group; and (4) elimination of bromide ion.

It has been reported that 2,6-dibromo-4,4-dimethylcyclohexanone (I) reacts with excess potassium acetate in hot acetic acid to give a compound formulated as 2-acetoxy-4,4-dimethylcyclohex-2-enone (II) plus 4,4-dimethylcyclohexane-1,2-dione (III).[2] Later,[3] the *cis* and *trans* forms of the 2,4-dibromo-9-methyl-3-decalones were described as undergoing comparable reactions. These formulations correspond to that made by Inhoffen[4] for a comparable reaction between 2,4-dibromocoprostan-3-one and potassium benzoate in a mixture of 1-butanol and toluene.



I II III

One possible explanation for the conversion of I to II is to assume an initial SN2′ displacement of bromine from the enol of I to form 2-acetoxy-2-bromo-4,4-dimethylcyclohexanone, which then undergoes elimination of hydrogen bromide to form II. Although there are certain seemingly related reactions, such as the formation of 4-α-acetoxycholestan-3-one from the reaction of potassium acetate in acetic acid with 2-α-bromocholestan-3-one, where SN2′ reactions of this type appear to be involved,[5] the postulate of an unusual reaction path applied to an intermediate that is present in only small concentration (the enol) seemed sufficiently novel to warrant further investigation. These re-

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[1] Allied Chemical Corporation Fellow, 1960–1961; Eastman Kodak Company Fellow, 1961–1962.

[2] M. Yanagita and A. Tahara, *J. Pharm. Soc. Japan*, **71**, 1060 (1951).

[3] M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); M. Yanagita and K. Yamakawa, *ibid.*, **22**, 291 (1957).

[4] H. H. Inhoffen, *Ann.*, **563**, 135 (1949).

[5] See E. L. Eliel, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 97, 98, and K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).