was filtered and washed with cold toluene followed by petroleum ether. The dried product (wt. 446 g., 90% yield) melted at 158–159° and was converted without further purification to *dl*-tryptophan in essentially the same yield as reported by Snyder and Smith.[3a]

Substitution of anhydrous sodium carbonate for sodium hydroxide in this reaction reduced the yield to 77.5%.

(2) **Solvent—Pyridine.**—A mixture of 19.7 g. of gramine, 24.5 g. of ethyl acetaminomalonate and 100 cc. of pyridine was refluxed for two hours in an atmosphere of nitrogen. The mixture was treated with Darco, filtered, concentrated to 50 cc. and diluted with 20 cc. of warm water. After storage at 5° for six hours an additional 80 cc. of water was added and the mixture was kept at 5° for eighteen hours. The product melted at 157–158° and weighed 18 g. (47.5%). The presence of 3 g. of powdered sodium hydroxide in the same size run increased the yield of product to 21.3 g. (54.6%). With smaller size runs (one-tenth size) yields as high as 73% were obtained.

When air was bubbled through the mixture during the reaction a deep red color was formed, the intensity of which increased with time. After such treatment none of the desired product could be isolated.

(3) **No Solvent.**—To 24.5 g. of molten ethyl acetaminomalonate at 150° was added 19.7 g. of gramine portionwise over a period of five to ten minutes. The temperature was raised during the addition to 165° and maintained there for ten minutes. The red oily product was cooled to 70°, dissolved in 70 cc. of alcohol and the solution was diluted with 50 cc. of warm water. After storage at 5° for eighteen hours the mixture was filtered, yielding 21.0 g. (54%) of product, m. p. 157–158°.

Gramine is unstable on heating above its melting point (131°); the decomposition is accompanied by the evolution of dimethylamine.

(b) **Condensation of Skatyldiethylamine with Ethyl Acetaminomalonate.**—A mixture of 36.8 g. of ethyl acetaminomalonate, 34.4 g. of skatyldiethylamine,[7] 150 cc. of toluene and 2 g. of powdered sodium hydroxide treated in the manner described in section (1) gave 50.6 g. (85.5%) of product melting at 156–158°.

(c) **Condensation with β-(N-piperidylmethyl)-indole.**—When ethyl acetaminoamalonate and β-(N-piperidylmethyl)-indole[8] were treated as in section (1), skatylaminomalonic ester was obtained in 64% yield; m. p., 157–158°.

Ethyl Skatylphthalimidomalonate.—A mixture of 3.5 g. of ethyl phthalimidomalonate, 2 g. of gramine, 0.3 g. of powdered sodium hydroxide and 15 cc. of toluene was refluxed for five hours. The evolution of dimethylamine appeared more sluggish than with ethyl acetaminomalonate. The filtered reaction mixture was kept cold for eighteen hours and filtered. The crude material (m. p. 120–145°) when recrystallized from ethanol gave 0.5 g. of light green crystals, m. p. 175–176°.

Anal. Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.50; H, 5.07. Found: C, 66.77; H, 4.99.

Acknowledgment.—The authors are indebted to Drs. R. T. Major and J. R. Stevens for their interest and valuable suggestions and to Mr. R. Boos and his associates for microanalyses.

Summary

Ethyl α-acetamino-α-carboethoxy-β-(3-indole)-propionate is made in excellent yields by direct condensation of gramine and ethyl acetaminomalonate, making possible the preparation of *dl*-tryptophan in 66% yields from indole. The condensation of other skatyldialkylamines with ethyl acetaminomalonate is described.

(7) Skatyldiethylamine was prepared from indole, formaldehyde and diethylamine by the method of Kuhn and Stein, *Ber.*, **70**, 567 (1937), in 93% yield. Our product (analytically pure) melts at 105°, rather than at 165° as recorded by Kuhn and Stein.

(8) β-(N-piperidylmethyl)-indole was prepared by refluxing a mixture of gramine and piperidine for three hours; yield, over 90%; m. p., 158–159°. *Anal.* Calcd. for: $C_{14}H_{18}N$: C, 78.50; H, 8.43; N, 13.10. Found: C, 78.35; H, 8.49; N, 12.93. We first obtained it by attempting to condense gramine and acetaminomalonic ester in the presence of piperidine.

RAHWAY, NEW JERSEY RECEIVED SEPTEMBER 6, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Preparation of Alkoxyacetaldehydes

BY LEWIS F. HATCH AND STUART S. NESBITT[1]

References to the preparation of alkoxyacetaldehydes have frequently appeared in the literature, but none has provided an entirely satisfactory laboratory method. The original method used was to treat halogen acetals with sodium alcoholates followed by acid hydrolysis of the alkoxyacetals.[2] Yields were low. Since β-alkoxyethyl alcohols have become commercially available, several methods for the preparation of alkoxyacetaldehydes have been proposed which depend upon either dehydrogenation[3] or oxidation[4] of these alcohols. Dehydrogenation was reported to give yields of 8–10% based on the starting materials while oxidation using chromic acid gave yields of 16.7 and 10% for methoxyacetaldehyde and ethoxyacetaldehyde.[4b] Redemann and Icke obtained a 30–35% yield of ethoxyacetaldehyde from cellosolve over a copper chromite catalyst at 310–330°.[3d] Somewhat higher yields are claimed in patented processes of a similar nature.

Lead tetraacetate and periodic acid will oxidize compounds having two hydroxyl groups attached to adjacent carbon atoms, and the oxidations are characterized by cleavage of the carbon–carbon bond to form carbonyl compounds.[5,6] Although this type of oxidation has been known for some time and the reactions used to prepare benzyloxy-

(1) From the M.A. thesis of S. S. Nesbitt, August, 1944. At present on active duty in the U. S. N. R.

(2) Rotbart, *Ann. chim.*, [11] **1**, 439 (1934), a review.

(3) (a) Drake, Duvall, Jacobs, Thompson and Sonnichsen, THIS JOURNAL, **60**, 73 (1938); (b) Drake, U. S. Patent 2,170,854 (1939); (c) Gresham, U. S. Patent 2,286,034 (1942); (d) Redemann and Icke, *J. Org. Chem.*, **8**, 159 (1943).

(4) (a) Malm, Nadeau and Diesel, U. S. Patent 2,000,604 (1935); (b) Hurd and Abernethy, THIS JOURNAL, **63**, 1966 (1941).

(5) Criegee, *Ber.*, **64**, 260 (1931).

(6) Malaprade, *Bull. soc. chim.*, [4] **43**, 683 (1928); *Compt. rend.*, **186**, 382 (1928).

acetaldehyde from glycerol α-benzyl ether,[7,8] no investigation has been reported of the application of these oxidations to the preparation of alkoxyacetaldehydes. The present study was made to ascertain whether this type of oxidation when applied to glycerol α-alkyl ethers would give a satisfactory laboratory method for the production of alkoxyacetaldehydes. The glycerol ethers are either available commercially or easily prepared by the reaction between the corresponding sodium alcoholate and glycerol α-monochlorohydrin[9] or by the reaction of the alcoholate with glycerol dichlorohydrin followed by hydrolysis of the alkyl ether of glycidol thus produced.[10] Both oxidizing agents are readily available.

The choice of oxidizing agents to be used is governed by the type of solvent employed. Water is the most suitable solvent for periodic acid while lead tetraacetate is better adapted to organic solvents such as benzene. The use of lead tetraacetate in benzene affords a means by which relatively water-insoluble alkoxyacetaldehydes can be produced anhydrous. When the alkoxyacetaldehydes are appreciably soluble in water, such as methoxy- and ethoxyacetaldehydes, the oxidation should be carried out in water using periodic acid as the oxidizing agent. Periodic acid may also be used to prepare less water soluble aldehydes[8]; however, it is felt that this procedure offers no advantages over that of using lead tetraacetate directly in an organic medium.

The difficulties which are encountered in the preparation of these aldehydes by the oxidation of glycerol α-alkyl ethers are inherent in the products and consequently are the same as those common to all other methods of preparation previously proposed. These difficulties arise mainly in the separation and isolation of the products from the reaction mixture and are caused by the tendency of the aldehydes to polymerize. If the aldehydes are to be separated from a water solution by distillation, it is necessary to make the solution neutral to methyl red. If they are to be separated from an organic solvent, low-temperature vacuum distillation is necessary.

Advantages in both periodic acid and lead tetraacetate oxidations are the completeness of the reaction and the absence of side reactions. A disadvantage for large-scale operation is the relative expense of the reagents.

Experimental

Lead Tetraacetate.—The lead tetraacetate was prepared from Pb_3O_4 (red lead) and acetic acid following the directions given by Oesper and Deasy.[11] The tetraacetate was recrystallized from acetic acid, filtered by suction and used without further removal of adhering acetic acid.

Periodic Acid.—The periodic acid was prepared as used from "Reagent" grade potassium periodate by carrying out the reaction in the presence of sulfuric acid.

(7) Sabetay, *Bull. soc. chim.*, [5] **2**, 1744 (1935).
(8) Palfray and Sabetay, *ibid.*, [5] **4**, 950 (1937).
(9) Davies, Heilbron and Owens, *J. Chem. Soc.*, 2542 (1930).
(10) Evans and Bullard, U. S. Patent 2,164,007 (1939).
(11) Oesper and Deasy, THIS JOURNAL, **61**, 972 (1939).

Glycerol α-Alkyl Ethers.—The following three glycerol α-alkyl ethers were obtained from Eastman Kodak Co., and were used without further purification: glycerol α-ethyl ether (b. p. 111–114° at 11 mm.); glycerol α-*n*-butyl ether (b. p. 118–121° at 7 mm.); glycerol α-phenyl ether (m. p. 48–53°). The following ethers were prepared by the reaction between glycerol α-monochlorohydrin and the corresponding alcohol using the procedure of Davies Heilbron and Owens.[9]

	B. p. °C. (cor.)	Mm.
Glycerol α-ethyl ether	92–94	5
Glycerol α-*n*-propyl ether	110–112	11
Glycerol α-isobutyl ether	110–112	4

Glycerol α-isobutyl ether has not been reported previously.

Glycerol α-Isobutyl Ether.—d^{25}_4 0.9911; $n^{25}D$ 1.4370; *MR* (calcd.) 39.22, (obsd.) 39.18. *Anal.* Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.45; H, 10.34.

Preparation of Alkoxyacetaldehydes

Oxidations Using Lead Tetraacetate.—Glycerol α-*n*-propyl, α-*n*-butyl and α-isobutyl ethers were oxidized by adding dropwise 0.50 mole of the ether to 0.50 mole of lead tetraacetate dissolved in 500 ml. of benzene in a 1-l. three-neck flask. During the addition and for one hour after the last of the ether had been added, the mixture was vigorously stirred and the temperature maintained between 25–30° by occasional cooling of the flask with ice-water.

The by-product lead acetate was removed by filtration and the filtrate extracted with three 100-ml. portions of water nearly saturated with salt. This extraction removed the by-product acetic acid while the salt decreased the solubility of the alkoxyaldehyde in the water. The benzene was removed at 40 mm. pressure through an 18-inch glass helix packed column. After removal of the solvent, the product was distilled at 100 mm. pressure. A center cut was taken for the determination of constants and to prepare a solid derivative. Yields and boiling points are in Table I.

TABLE I

PREPARATION OF ALKOXYACETALDEHYDES $ROCH_2CHO$

R	Oxidizing agent	Yield, %	Boiling point, (cor.), °C.	Pressure, mm.
CH_3	HIO_4	51	88–89[a]	Atm.
C_2H_5	HIO_4	40	90–91[a]	Atm.
n-C_3H_7	$Pb(OAc)_4$	28	68[b]	100
n-C_4H_9	$Pb(OAc)_4$	57	87	100
iso-C_4H_9	$Pb(OAc)_4$	61	73[c]	100
Phenyl	$Pb(OAc)_4$	45	94	6

[a] Azeotrope with water. [b] 118–119° at 748 mm. [c] 130–131° at 745 mm.

This procedure was not satisfactory for the production of either methoxy- or ethoxyacetaldehydes because of their solubility in water.

With glycerol α-phenyl ether 0.25 mole of the ether was dissolved in 150 ml. of benzene and added dropwise to 500 ml. of benzene containing 0.25 mole of the tetraacetate. The rest of the procedure was similar to that used for the alkyl ethers except that the acetic acid was extracted using water followed by dilute sodium bicarbonate solution, then water again. The benzene was removed as previously noted and the phenoxyacetaldehyde distilled at 94° under 6 mm. pressure.

It was not possible to determine the indices of refraction of these alkoxyacetaldehydes with accuracy because the readings changed rapidly while in contact with the prisms of the Abbe refractometer. The values which are given may be considered as close approximations.

***n*-Propoxyacetaldehyde.**—2,4-Dinitrophenylhydrazone, m. p. 86° (cor.). *Anal.* Calcd. for $C_{11}H_{14}O_5N_4$: N, 19.86. Found: N, 19.98.

***n*-Butoxyacetaldehyde.**—d^{25}_4 0.9199; $n^{25}D$ 1.4148; *MR* (calcd.) 31.56; (obsd.) 31.59; semicarbazone m. p. 100° (cor.). *Anal.* Calcd. for $C_7H_{15}O_2N_3$: N, 24.24. Found: N, 24.21.

Isobutoxyacetaldehyde.—d^{25}_4 0.9214; $n^{25}D$ 1.4080; *MR* (calcd.) 31.56; (obsd.) 31.09; semicarbazone m. p. 136° (cor.). *Anal.* Calcd. for $C_7H_{15}O_2N_3$: N, 24.24. Found: N, 24.39.

Phenoxyacetaldehyde.—Semicarbazone m. p. 146° (cor.) (literature[2] 145°); 2,4-dinitrophenylhydrazone m. p. 138° (cor.).

Oxidations Using Periodic Acid.—One-half mole of the ether (either glycerol α-methyl or α-ethyl ether) was added dropwise to a solution of 0.50 mole of potassium periodate and 12 g. of sulfuric acid in 400 ml. of water in a 1-liter three-neck flask. The mixture was vigorously stirred during the addition of the ether and for two hours after addition was complete. The temperature was maintained between 25–30°. The mixture was then filtered to remove the precipitated potassium iodate. The filtrate was neutralized to a methyl red end-point with sodium hydroxide; then sufficient barium chloride was added to remove the iodate and the sulfate ions as barium salts. It is necessary to remove the iodate ion to prevent further oxidation of the product during subsequent distillation.

With methoxyacetaldehyde, the filtrate, after removal of the barium salts, was distilled through an 18-inch helix packed column and a 50-ml. fraction boiling 88–98.5° obtained. This fraction was refractionated through a 4 ft. helix packed column and 21.5 g. of the azeotrope with water (88–89°) was obtained. This represents a yield of 51% since the azeotrope contains 12.8% water.[3] With ethoxyacetaldehyde the filtrate gave, without redistillation, 22.5 g. of a water azeotrope boiling 90–91°. This represents a yield of 40% since the azeotrope contains 21.8% water.[3]

The methoxyacetaldehyde gave a 2,4-dinitrophenylhydrazone melting at 124°. The ethoxyacetaldehyde gave a 2,4-dinitrophenylhydrazone melting at 116°.

Summary

1. Methoxy- and ethoxyacetaldehydes have been prepared by the oxidation of the corresponding glycerol α-alkyl ethers using periodic acid.

2. *n*-Propoxy-, *n*-butoxy-, isobutoxy- and phenoxyacetaldehydes have been prepared by the oxidation of the corresponding glycerol α-alkyl ethers using lead tetraacetate, and several of their properties were determined.

3. Glycerol α-isobutyl ether was prepared and characterized.

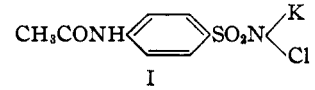
AUSTIN, TEXAS RECEIVED AUGUST 25, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

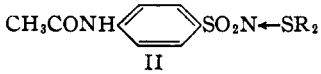
Arsinimines Derived from Sulfanilamide. The Condensation of Triaryl Arsines and Arsine Oxides with Sulfanilamide and its Derivatives

BY D. S. TARBELL AND JAMES R. VAUGHAN, JR.[1]

In a previous article[2] methods were described for the preparation of N^1-potassiochloro-N^4-acetylsulfanilamide (I) and similar compounds from N^4-acetylsulfanilamide, and it was found that compounds of this type would condense with organic sulfides to form sulfilimines (II). Furthermore, it has been reported by Mann[3] that triarylarsines and their oxides condense with chloramine-T and *p*-toluenesulfonamide, respectively, to yield the corresponding arsinimines, either in the hydrated form (III) or as the anhydrous arsinimines (IV).



I



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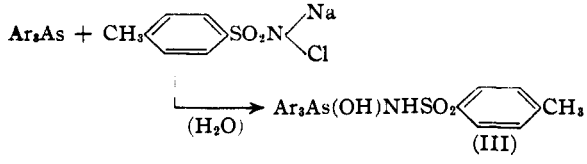

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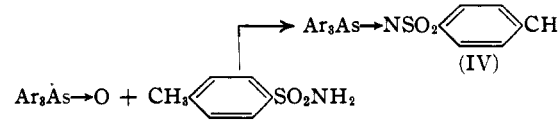
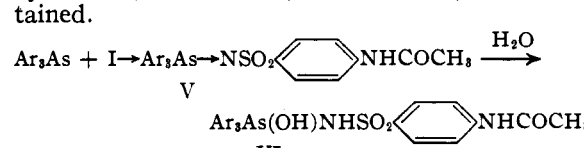


In view of the possible bacteriological importance of compounds of this type, we have prepared a number of arsinimines derived from sulfanilamide by these general methods. Results from tests on these compounds for both arsenic and sulfanilamide type effects will be reported elsewhere.

Two methods of preparation were used. In the first method, triarylarsines were condensed with I under mild conditions in anhydrous solvents to yield the corresponding arsinimines (V) which were usually isolated in the hydrated form (VI) under the conditions of the reaction. In only one case, using tri-*p*-tolylarsine, was the arsinimine (VII) isolated in the anhydrous form. With triphenylarsine or tri-*o*-tolylarsine, only the hydrated arsinimines (VIII and IX) were obtained.



VII, Ar = *p*-$CH_3C_6H_4$
VIII, Ar = C_6H_5
IX, Ar = *o*-$CH_3C_6H_4$

(1) Present address: American Cyanamid Company, Stamford, Connecticut.

(2) Todd, Fletcher and Tarbell, THIS JOURNAL, **65**, 350 (1943).

(3) (a) Mann, *J. Chem. Soc.*, 958 (1932); (b) Mann and Chaplin, *ibid.*, 527 (1937).