and ethyl alcohols. In a few cases where the hydrochloride was only very slightly soluble in water, the picrate was prepared by adding an excess of alcoholic picric acid solution to an alcoholic solution of the hydrochloride. The picrate was allowed to crystallize, then was washed with water and recrystallized from ethyl alcohol after air drying.

Invert Soaps.—The quaternary methosulfates were prepared by refluxing equivalent quantities of the free base and di-methyl sulfate and half the total volume of dry benzene for four hours. They were finally crystallized from methyl alcohol or ethyl acetate.

The melting points were determined on Fisher–Johns electrical melting point apparatus, and the point of complete liquefaction was determined.

Acknowledgment.—The authors desire to express their appreciation to the Commanding Officer of Edgewood Arsenal for the mustard gas, and to the Chemical Division of Armour and Company for the amines used in this work.

Summary

Studies in the utilization of mustard gas for peace time industrial purposes have now been extended also to its oxidation products. Thus far, these compounds were used in the preparation of a series of "invert soaps" containing a thiamorpholine nucleus and possessing rather promising properties.

EASTON, PA.
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NOTES

The Reversible Inactivation of Gliotoxin by Thiols

BY CHESTER J. CAVALLITO, JOHN HAYS BAILEY AND WILLIAM F. WARNER

In a recent publication, Dutcher, Johnson and Bruce[1] reported results at variance with the observation[2] that cysteine inactivates gliotoxin. The inactivation of gliotoxin has been investigated with a number of thiols at several *p*H values and is readily observable when antibacterial activity is tested by both the dilution and the cylinder-plate method. In any inactivation studies of this type one obviously includes control tests which would determine the inactivating action of *p*H alone.

Dilute solutions of gliotoxin buffered at *p*H values of 6, 7 or 8 rapidly lost their antibacterial activity when treated with an excess of cysteine, N-acetylcysteine or thioglycolate, but not with S-methylcysteine. Longer standing than ten minutes prior to testing produced no further inactivation. When the reaction mixture was allowed to stand in air rather than under nitrogen, antibacterial activity as measured by the plate method, was slowly regenerated. Addition of more thiol again eliminated this activity. It therefore appeared that the thiol inactivation of gliotoxin was reversible by oxidation. This could be shown by treating gliotoxin with cysteine to produce an inactive mixture which after titration with iodine solution (to the starch–iodine end-point) showed complete regeneration of antibacterial activity.

The observed reversible inactivation of gliotoxin by means of reactive thiol compounds favors the dithio structures for gliotoxin rather than the thiosulfinate structure, which latter should not be capable of reversible reduction–oxidation. Whether gliotoxin is merely reduced to the dithiol structure or forms an intermediate product with the inactivating thiol was not shown, as a result of limited quantities of the antibiotic available. However, it would appear that the reaction represents an equilibrium between active (oxidized or dithio-) gliotoxin and inactive (reduced or dithiol-) gliotoxin and the thiol and dithio forms of the inactivator. This would be in agreement with the observed reaction[1] of gliotoxin with alkaline thioglycolate.

The reaction of gliotoxin with thiol groups is in agreement with our postulated mode of action for a large group of antibiotics and would be an example of method 1 (oxidation) discussed in an earlier paper,[3] in which an antibiotic disulfide could oxidize —SH groups essential to certain enzymes to enzyme —S—S— groups.

The failure of Dutcher, Johnson and Bruce to observe the reaction of cysteine with gliotoxin might result from testing for antibacterial action under conditions which would allow reoxidation of reduced gliotoxin to the active dithio-form.

Experimental

Gliotoxin was dissolved in a minimum of ethanol, and diluted with 0.5 *M* potassium phosphate buffer of the *p*H desired. The thiol compound was also dissolved in 0.5 *M* phosphate buffer of corresponding *p*H values. The two solutions were mixed so that each cc. of mixture contained 0.1 mg. of gliotoxin, not more than 5% ethanol and variable quantities of the thiol. The mixture was allowed to stand at room temperature for various periods of time, then tested for antibacterial activity against *Staphylococcus aureus* by the usual dilution and cylinder-plate methods. Buffer alone at *p*H of 6, 7 or 8 produced no loss of antibacterial activity in twenty-four hours; 0.1 mg. per cc. of cysteine produced a noticeable loss, 0.4 mg. per cc., nearly complete loss and 1.0 mg. per cc., total loss of antibacterial activity after ten minutes reaction time.

(1) Dutcher, Johnson and Bruce, THIS JOURNAL, **67**, 1736 (1945).
(2) Cavallito and Bailey, *Science*, **100**, 390 (1944).
(3) Cavallito, Bailey, Haskell, McCormick and Warner, *J. Bact.*, **50**, 61 (1945).

Further reaction time (up to twenty-four hours) did not produce significant changes. Under similar conditions, N-acetylcysteine and thioglycolate also inactivated gliotoxin, whereas 10 mg. per cc. of S-methylcysteine had no effect.

The antibacterial activity of reduced gliotoxin could be regenerated immediately by titration with iodine solution or slowly by exposure to oxygen.

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Catalytic Conversion of Aldols over Chromia Catalysts

BY J. R. COLEY AND V. I. KOMAREWSKY

Recently it has been shown[1] that branched aldehydes having an *alpha*-substituted carbon atom do not undergo the complex dehydrogenation-condensation reactions when subjected to catalytic conversion over a chromia catalyst at 400° to give either ketones and olefins or unsaturated aldehydes. This was unexpected since the catalytic condensation had been assumed to be similar to a conventional liquid phase aldol condensation.

It has therefore been of interest to examine the behavior of several aldols when subjected to these conditions.

Procedure.—The aldols were prepared by the procedure of Batalin and Slavina.[2] They were vaporized and passed over a chromia catalyst at 400° in a vertical furnace at a space velocity of 0.1 as previously described.[3] The products were distilled in a 36-inch super-cal Heli Grid Podbielniak Column.

Results.—The results obtained are given in the following table.

Aldol	Ketone	B. p., °C.	Yield, %
$CH_3CH(OH)C(CH_3)_2CHO$	$CH_3COCH(CH_3)_2$	95	12.0[a]
$(CH_3)_2CHCHOHC(CH_3)_2CHO$	$[(CH_3)_2CH]_2CO$	124	6.5[b]
$(C_2H_5)CH_3CHOHCH(C_2H_5)CHO$	$(C_2H_7)_2CO$	144	61.0[c]
$(C_4H_9)CH_3CHOHCH(C_4H_9)CHO$	$(C_6H_{13})_2CO$	[e]	82.8[d]

[a] 2,4-Dinitrophenylhydrazone, m. p. 116–117°. [b] 2,4-Dinitrophenylhydrazone, m. p. 85–86°. [c] Semicarbazone, m. p. 134–135°. [d] Dihexylcarbinol, m. p. 40.0–40.5°. [e] M. p. 32.0–32.5°.

These results indicate that the step blocking the conversion of *alpha*-substituted aldehydes is not the primary condensation step but the secondary decarbonylation and dehydrogenation step. The major product obtained from the catalytic conversion of the aldols of *alpha*-substituted aldehydes was the original aldehyde. This is the product normally expected from thermal decomposition of aldols.

DEPARTMENT OF CHEMICAL ENGINEERING
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO, ILLINOIS RECEIVED DECEMBER 28, 1945

(1) V. I. Komarewsky and L. G. Smith, THIS JOURNAL, **66**, 1116 (1944).

(2) V. S. Batalin and S. E. Slavina, *J. Gen. Chem. U. S. S. R.*, **7**, 202 (1937).

(3) V. I. Komarewsky and J. R. Coley, THIS JOURNAL, **63**, 709, 3269 (1941); V. I. Komarewsky and T. H. Kritchevsky, *ibid.*, **65**, 547 (1943).

The α-Naphthyl Isocyanate Derivative of *n*-Butylaniline[1]

BY DAVID CRAIG

Kharasch, Richlin and Mayo[2] have described the reaction of butyraldehyde with aniline to produce *n*-butylaniline among other products. They reported that α-naphthyl isocyanate[3] reacted with this *n*-butylaniline as well as with a known sample to form N-*n*-butyl-N-phenyl-N′-α-naphthylurea.

We have found that equivalent weights of the *n*-butylaniline and α-naphthyl isocyanate do react to form almost the theoretical yield of the expected urea which, however, instead of melting at 277° as stated by Kharasch, *et al.*, actually melts at 97–98°. A mixed melting point of this derivative with that prepared from *n*-butylaniline isolated from the reaction of butyraldehyde with aniline showed no depression. Hexane was a satisfactory solvent for recrystallization.

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.20; H, 6.98; N, 8.79. Found: C, 79.18, 79.23; H, 7.01, 6.95; N, 8.67, 8.78.

The single analysis reported by Kharasch and others was 9.03 for nitrogen. This value which is in excellent agreement with 8.97, the nitrogen content of N,N′-di-α-naphthylurea, and the very high melting point of 277° reported by them suggest that under their conditions of reaction, water may have been present or a disproportionation of the expected urea may have occurred. In either case N,N′-di-α-naphthylurea would be expected as a product. The formation of this urea is sometimes troublesome when conducting reactions of α-naphthyl isocyanate with amines in the presence of tertiary amines.[2] Thus *n*-butylaniline (2.0 g.) and 3-ethyl-2-propylquinoline (0.5 g.) reacted with the isocyanate (1.7 g.) at room temperature to form small amounts of N,N′-di-α-naphthylurea, N-*n*-butyl-N-phenyl-N′-α-naphthylurea and presumably N,N′-di-*n*-butyl-N,N′-diphenylurea reported by Wahl.[4] In a subsequent experiment 0.8 g. of N-*n*-butyl-N-phenyl-N′-α-naphthylurea was heated for two hours at 100° with 0.4 g. of 3-ethyl-2-propylquinoline. By extraction with hexane 0.1 g. of N,N′-di-α-naphthylurea was obtained. Fortunately N,N′-di-α-naphthylurea is easily isolated due to its extreme insolubility in hexane and other solvents. It melts when pure at 296°. The investigation described here suggests that one feature of the effect of tertiary amines on the reaction of α-naphthyl isocyanate with other amines is the formation of N,N′-di-α-naphthylurea.

RESEARCH LABORATORY
B. F. GOODRICH CO.
AKRON, OHIO RECEIVED DECEMBER 26, 1945

(1) Editor's footnote.—A copy of this Note was sent on its receipt to Dr. M. S. Kharasch for his information. In reply Dr. Kharasch promptly submitted the following statement for publication: "The writer has been aware for a few years that through an error on his part (and not of his co-workers) the melting point of the derivative of *n*-butylaniline with α-naphthyl isocyanate (isolated in the reaction of *n*-butyraldehyde and aniline) had been incorrectly reported [Kharasch, Richlin and Mayo, THIS JOURNAL, **62**, 497 (1940)]. Due to pressure of other work this oversight had not been corrected. The melting point of the derivative as obtained by us was 87–89°. By some unexplainable lapse of intelligence, the melting point of the N,N′-di-α-naphthylurea prepared in the course of that work was confused in the writing of the text with that of N-*n*-butyl-N-phenyl-N′,α-naphthylurea. The writer is grateful to Dr. Craig for making the appropriate correction, but he wishes to point out that none of the results or conclusions of that article are thereby invalidated." M. S. KHARASCH.

(2) Kharasch, Richlin and Mayo, THIS JOURNAL, **62**, 497 (1940).

(3) French and Wirtel, *ibid.*, **48**, 1736 (1926).

(4) Wahl, *Bull. Soc. Chim.*, [5] **1**, 246 (1934).