

been 2,3 in one or both compounds, a shift stemming from the 2- vs. the 3-methoxyl would have been expected. The existence of only one line therefore supports the 2,5 rather than the 2,3 relationship in these cyclic ketals and establishes the stereo-isomeric relationship VIIb and VIIIb.

### Experimental

*cis-trans*-Dibenzoylstilbene equilibrations of 1-g. samples in 750 ml. of 95% ethanol were carried out under reflux and an atmosphere of nitrogen (see table). For the base-catalyzed equilibrations, hot 86% aqueous potassium hydroxide was added to achieve the specified weight-per cent concentrations. After heating, the solutions were poured into 12 l. of ice water and the mixtures were allowed to stand overnight. The precipitates were filtered, washed, dried, dissolved in benzene, and chromatographically separated (see below). The irradiation experiments in 95% ethanol were carried out at reflux in strong sunlight; work-up of these solutions, however, was by evaporation to ca. 30 ml., seeding with *trans* isomer, allowing to stand overnight, filtering the crop of *trans* crystals, evaporating the filtrate to dryness, dissolving the residue in benzene, and chromatographing.

The benzene solutions of the mixture of isomers were poured through an F-20 alumina column, eluting the higher-melting *trans* isomer with benzene. Acetone was then used to elute the more soluble yet more highly adsorbed *cis* isomer. Evaporation of the solutions gave pure *cis* and *trans* isomers of m.p. 212–214° and 230–232°, respectively, in total yields given in Table I. Systematic efforts were not made to work up the by-products of the reactions.

In separate experiments both the *cis* and *trans* isomers were passed on alumina columns and eluted in the above way. The samples were recovered unchanged, showing that no

isomerization or extensive deterioration occurred under work-up conditions.

TABLE I  
*cis-trans* EQUILIBRATIONS

| Equilibrating agent, 95% ethanol <sup>a</sup>                            | Time <sup>b</sup> required, hr. | % Yield of mixture <sup>c</sup> |                   | <i>cis-trans</i> equilibrium ratios |                   |
|--|---------------------------------|---------------------------------|-------------------|-------------------------------------|-------------------|
|  |                                 | from <i>cis</i>                 | from <i>trans</i> | from <i>cis</i>                     | from <i>trans</i> |
| KOH, 10%   | 3.5                             | 77                              | 88                | 78:22                               | 78:22             |
| 2.9%   | 12                              | 73                              | 77                | 55:45                               | 56:44             |
| 0.71%  | 36                              | 73                              | 68                | 42:58                               | 43:57             |
| 0.022% <sup>d</sup>  | 168                             | 84                              | 88                | 44:56                               | 41:59             |
| h $\nu$  | 4                               | 58                              | 46                | 33:67                               | 31:69             |
| h $\nu$ (C <sub>6</sub> H <sub>6</sub> ) <sup>e</sup>                    | 48                              | 64                              | 42                | 32:68                               | 34:66             |
| h $\nu$ (C <sub>6</sub> H <sub>6</sub> , I <sub>2</sub> ) <sup>e,f</sup> | 48                              | 52                              | 66                | 32:68                               | 35:65             |

<sup>a</sup> Used except in the last two photoequilibrations. <sup>b</sup> These times might have been shortened somewhat. <sup>c</sup> The mixtures represent the bulk of crystalline materials obtained which contained only the pure stereoisomers; these were much less soluble than the by-products. Although the losses were considerable, it can be said that little of the more soluble *cis* isomer escaped, and these figures seem to be reasonably accurate. <sup>d</sup> This represents a 1:1 molar ratio of base to compound. To have cut the concentration further would have been impractical because of the concomitant drop in reaction rate. <sup>e</sup> One gram of compound per 700 ml. of benzene, at room temperature. <sup>f</sup> Crystals of iodine were introduced periodically to maintain a small amount throughout the reaction, for the purpose of determining its effect, if any.

**Acknowledgment.**<sup>1c</sup>—The n.m.r. spectra and interpretations were furnished by E. G. Brame, Experimental Station, du Pont Co.

## Azo and Hydrazo Aliphatic Acid Derivatives. I. Alkylazoformic Acid Esters<sup>1</sup>

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The ethyl esters of *n*- and *t*-butylazoformic acid have been synthesized and some of their properties have been recorded.

As part of a program designed to synthesize derivatives of azo and hydrazo aliphatic acids of the general formulas R(CH<sub>2</sub>)<sub>x</sub>N=N(CH<sub>2</sub>)<sub>y</sub>CO<sub>2</sub>H and R(CH<sub>2</sub>)<sub>x</sub>NHNH(CH<sub>2</sub>)<sub>y</sub>CO<sub>2</sub>H as possible anticancer agents, it appeared to be of interest to investigate esters of azoformic acid. The latter, which would be represented by the case where *y* = 0 in the first general formula, should be obtainable from alkylidene carbazates, which result from the condensation of carbonyl compounds with alkyl carbazates,<sup>2</sup> by reduction, followed by oxidation of the intermediate hydrazo esters.

In the present work, 1-*n*-butyl-2-carbethoxy-

hydrazine was selected as a representative hydrazo ester for oxidation studies. It was thought that the carbethoxy group might stabilize the azo structure. As is known,<sup>3</sup> aliphatic azo compounds which have at least one hydrogen atom at an  $\alpha$ -carbon tend to rearrange to the isomeric hydrazones. O'Connor<sup>4</sup> has shown recently that phenylhydrazones of aliphatic ketones and aldehydes are converted rapidly in solution to the azo tautomers.

The oxidation of 1-*n*-butyl-2-carbethoxyhydrazine by means of bromine water at temperatures below 0° afforded a yellow liquid with a sweet odor which showed an absorption maximum near 375

(1) It is a pleasure to acknowledge the support of this research through Research Grant CY-4662 from the Cancer Chemotherapy National Service Center, National Cancer Institute, U.S. Public Health Service.

(2) N. Rabjohn and H. D. Barnstorf, *J. Am. Chem. Soc.*, **75**, 2259 (1953).

(3) For leading references see: H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961, p. 327. N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 434.

(4) R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

$m\mu$  of low intensity. Several aliphatic azo compounds have been found<sup>5</sup> to exhibit weak absorptions in the region of 345–360  $m\mu$ . The ester group in conjugation with the azo double bond might be expected to cause a bathochromic shift of this absorption band. The ethyl *n*-butylazocarboxylate isomerized fairly rapidly at room temperature to *n*-butylaldehydecarbethoxyhydrazine. The ethanol solutions of the azo ester which were used for the ultraviolet absorption studies appeared to be more stable.

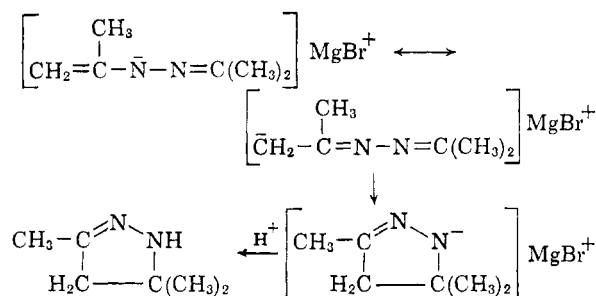
The synthesis of ethyl *t*-butylazocarboxylate was undertaken then in order to obtain a more stable ester of azoformic acid. Efforts to prepare the needed intermediate hydrazine from ethyl carbazate by condensation with *t*-butyl chloride or *t*-butyl alcohol in the presence of sulfuric acid were fruitless. It was synthesized successfully from *t*-butylhydrazine and ethyl chloroformate; obviously steric factors were in large part responsible for the introduction of the carbethoxy grouping on the less basic nitrogen atom of the substituted hydrazine. The 1-*t*-butyl-2-carbethoxyhydrazine was oxidized by silver oxide in benzene solution to the desired azo ester. The latter has an ultraviolet absorption maximum at 378  $m\mu$  ( $\epsilon_{\max}$  31.1) and a weak absorption band in the infrared at 1635  $\text{cm}^{-1}$ . Lieber and co-workers<sup>6</sup> have found absorptions in the range of 1631–1613  $\text{cm}^{-1}$  for some azo compounds. We have observed also a weak absorption at 1610  $\text{cm}^{-1}$  in the infrared spectrum of ethyl azodicarboxylate.

Ethyl *t*-butylazocarboxylate appears to be stable up to 170°, but decomposes readily in the presence of a trace of acid.

The *t*-butylhydrazine employed in the preparation of the 1-*t*-butyl-2-carbethoxyhydrazine was obtained in low yield by the alkylation of hydrazine with *t*-butyl chloride according to the method of Westphal.<sup>7</sup> Attempts to synthesize *t*-butylhydrazine by treating acetone azine with methylmagnesium bromide in the manner reported by Klages, *et al.*,<sup>8</sup> led to unexpected results. The product, which was a mixture, was treated with hydrogen chloride, and the mixture of salts was separated by fractional crystallization. There were isolated 18% of 3,5,5-trimethyl-2-pyrazoline hydrochloride, a large amount of hydrazine hydrochloride and only 3.4% of *t*-butylhydrazine hydrochloride, instead of the claimed 30–60%.

It was observed that a gas was evolved when acetone azine was added to methylmagnesium bromide. A Zerevitinov determination<sup>9</sup> on pure ace-

tone azine in amyl ether at 100° indicated that 1.3 mole equivalents of methane was evolved and that 0.5 mole equivalent of methylmagnesium iodide added to the azine. It is known<sup>10</sup> that aliphatic or aliphatic-aromatic ketoanils react as though they exist in the tautomeric enamic form. The formation of 3,5,5-trimethyl-2-pyrazoline from acetone azine and methylmagnesium bromide might take place according to the following scheme.



The results of tests of the compounds described against animal tumors will be reported elsewhere.

### Experimental<sup>11</sup>

***n*-Butylaldehydecarbethoxyhydrazine.**—A mixture of 52 g. (0.5 mole) of ethyl carbazate, 39.6 g. (0.55 mole) of *n*-butylaldehyde, 100 ml. of absolute alcohol, and 0.5 ml. of acetic acid was heated to boiling and allowed to stand overnight. The solvent was removed, and the residue was distilled to give an almost quantitative yield of product; b.p. 113–114°/2 mm., m.p. 47–48°.

*Anal.* Calcd. for  $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$ : C, 53.14; H, 8.92. Found: C, 53.53; H, 8.81.

**1-*n*-Butyl-2-carbethoxyhydrazine.**—A solution of 47.4 g. (0.3 mole) of *n*-butylaldehydecarbethoxyhydrazine in 270 ml. of 95% ethanol and 30 ml. of acetic acid was added to 0.9 g. of prerduced platinum oxide catalyst, and the mixture was shaken with hydrogen at 50 p.s.i. overnight. The catalyst was removed by filtration, the solvents were evaporated, and the residue was taken up in ether. The solution was washed with 10% sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 42.2 g. (86%) of the substituted hydrazine (b.p. 78–79°/1 mm.) which solidified upon standing, m.p. 34–35°.

*Anal.* Calcd. for  $\text{C}_7\text{H}_{16}\text{N}_2\text{O}_2$ : C, 52.47; H, 10.07. Found: C, 52.80; H, 9.80.

**Oxidation of 1-*n*-Butyl-2-carbethoxyhydrazine.**—A mixture of 16 g. (0.1 mole) of 1-*n*-butyl-2-carbethoxyhydrazine and 100 ml. of a saturated salt solution was cooled to –15° and stirred while saturated bromine water, which contained 17.6 g. of bromine, was added over a period of 3.5 hr. The reaction mixture was stirred for an additional 2 hr. by which time it was yellow, and 275 ml. of gas had been evolved.

The mixture was extracted with ether, and the ethereal solution was washed with sodium bicarbonate solution and dried over sodium sulfate. The solvent was removed at 0° under reduced pressure, and the yellow residue was dissolved in pentane. The latter solution was cooled in Dry Ice

(5) A. Buraway, *J. Chem. Soc.*, 1865 (1934); C. G. Overberger, M. T. O'Shaughnessy, and H. Shalit, *J. Am. Chem. Soc.*, **71**, 2663 (1949); D. C. Iffland, L. Salisbury, and W. R. Schafer, *ibid.*, **83**, 747 (1961).

(6) E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951); see also L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London, 2nd ed., 1958, p. 272.

(7) O. Westphal, *Ber.*, **74B**, 759 (1941).

(8) F. Klages, G. Nober, F. Kircher, and M. Bock, *Ann.*, **547**, 24 (1941).

(9) H. E. Zaugg and W. M. Lauer, *Anal. Chem.*, **20**, 1022 (1948).

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1208.

(11) The melting points and boiling points are uncorrected. The carbon-hydrogen analyses were performed by Drs. Weiler and Strauss, Oxford, England.

and a solid separated which was shown to be *n*-butyraldehyde-carbethoxyhydrazone by a comparison of infrared spectra and a mixed melting point determination.

The solution was diluted then with ether, washed repeatedly with 2 *N* hydrochloric acid, followed by sodium bicarbonate solution and water. After drying the solution and removing the solvents under reduced pressure at 0°, there was obtained 2.2 g. of a yellow liquid which possessed a sweet odor. It was stored at Dry Ice temperatures. An ethanol solution of this material showed a weak absorption maximum near 375  $m\mu$ ; no maximum was observed at 220  $m\mu$ . A sample of the compound was allowed to stand at room temperature and after a few hours an absorption maximum developed at 220  $m\mu$  which indicated the presence of an hydrazone. Upon working up this sample, a solid was obtained which had an infrared spectrum identical with that of *n*-butyraldehyde-carbethoxyhydrazone.

***t*-Butylhydrazine Hydrochloride.**—Essentially the method of Westphal<sup>7</sup> was followed. From 60 g. (1.9 moles) of anhydrous hydrazine and 180 g. (1.9 moles) of *t*-butyl chloride in 150 ml. of methanol there was obtained 12.1 g. (5%) of *t*-butylhydrazine hydrochloride which melted at 192–194° after repeated recrystallizations from methanol. Comparable yields of the hydrochloride were realized when the reaction was carried out in the presence of dimethylformamide. The yield was lowered slightly when dioxane was used as the solvent in the reaction.

**1-*t*-Butyl-2-carbethoxyhydrazine.**—A solution of 7.47 g. (0.06 mole) of *t*-butylhydrazine hydrochloride in 5 ml. of water was neutralized with 2.4 g. (0.06 mole) of sodium hydroxide in 3.6 ml. of water. This was added to a mixture of 20 ml. of pyridine and 80 ml. of water, and 6.5 g. (0.06 mole) of ethyl chloroformate was added dropwise with stirring. After all had been added, the reaction mixture was stirred for an additional hour, and then was extracted re-

peatedly with ether. The ether solution was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was fractionated to give 6.3 g. (66%) of material which boiled at 75–77°/2–3 mm. and melted at 24–25°.

*Anal.* Calcd. for  $C_7H_{16}N_2O_2$ : C, 52.47; H, 10.07. Found: C, 52.87; H, 10.12.

**Ethyl *t*-Butylazocarboxylate.**—A mixture of 1.6 g. (0.01 mole) of 1-*t*-butyl-2-carbethoxyhydrazine, 0.8 g. of anhydrous magnesium sulfate, and 10 ml. of benzene was stirred in an ice bath and 1.5 g. of silver oxide was added. Stirring was continued for 1 hr. at 20°, a further 1.5 g. of silver oxide was added, and the reaction was maintained for another hour. The mixture was filtered, the residue was washed with ether, and the combined solutions were evaporated to leave 1.4 g. of residue. This was purified by evaporative sublimation at room temperature at 0.7 mm. pressure. The material had a sweet odor, was yellow and a middle fraction boiled at 168–170°; m.p., –33 to –32°,  $n_D^{25}$  1.4155,  $d_4^{25}$  0.9317, molecular refractivity 42.48, calculated 42.56 (using the constants of Barrick, *et al.*,<sup>12</sup> for aliphatic azo compounds.

*Anal.* Calcd. for  $C_7H_{14}N_2O_2$ : C, 53.14, H, 8.92. Found: C, 53.32, 53.45; H, 9.52, 9.36.

A sample of the azo compound was heated under nitrogen in a flask attached to a gas buret. No appreciable change in volume was observed up to a bath temperature of 170°. The infrared spectrum of the heated residue was identical with that of the original material. The experiment was repeated in the presence of a small amount of *p*-toluenesulfonic acid. It was observed that a gas was evolved slowly even at room temperature under these conditions.

(12) L. D. Barrick, G. W. Drake, and H. L. Lochte, *J. Am. Chem. Soc.*, **58**, 160 (1936).

## Nitrosoanilines. II

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A variety of *N*-substituted *p*-nitrosoanilines were prepared by standard methods. A number of bulky groups such as phthalimido and benzothiazolythio have been incorporated as the aniline *N*-substituents. The phthalimidomethyl group contributes measurably to increased stability.

The chemical modification of butyl rubber with *N*, 4-dinitroso-*N*-methylaniline<sup>1</sup> to give filled vulcanizates with greatly improved properties<sup>2</sup> made it advisable to prepare new nitrosoanilines, preferably with higher melting points and exhibiting increased thermal stability. The initial phase of this investigation, as reported in a previous paper,<sup>3</sup> included the preparation of a variety of compounds possess-

ing the general formula  $ON\langle\text{C}_6\text{H}_4\rangle\text{N}\begin{matrix} R' \\ | \\ -R \end{matrix}$ , wherein X = H, Cl, and  $-\text{OC}_2\text{H}_5$ ; R and R' = H, alkyl

alkenyl,  $-\text{CH}_2\text{C}_2\text{H}_4\text{CN}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{Cl}$ , acid esters, and hetero groups.

The work reported herein involves the preparation of nitrosoanilines with R representing much larger or bulky groups. Inasmuch as the intermediates required for these preparations were not available, the synthesis of such substituted anilines was necessitated. These were of two general classes; (1) imide-formaldehyde-amine condensation products and (2) phthalimide- or 2-mercaptobenzothiazole-chloroamine reaction products. The first class was prepared by the procedures described by Winstead, Heine, and Blair<sup>4,5</sup> to give compounds of

(1) Currently available in 33-1/3% active mixture with an inert filler under the Monsanto Chemical Co. tradename "Elastopar."

(2) H. M. Leeper, C. I. Gable, J. J. D'Amico, and C. C. Tung, *Rubber World*, **135**, 413 (1956).

(3) J. J. D'Amico, C. C. Tung, and L. A. Walker, *J. Am. Chem. Soc.*, **81**, 5957 (1959).

(4) M. B. Winstead and H. W. Heine, *J. Am. Chem. Soc.* **77**, 1913 (1955).

(5) H. W. Heine, M. B. Winstead, and R. P. Blair, *J. Am. Chem. Soc.* **78**, 672 (1956).