ing the course of single experiments with the more dilute catalyst solutions.

The three results with heterogeneous systems are probably of little more than qualitative interest. Despite the complexity of the systems, solution of the copolymerization equation yielded reasonable values for r_1 and r_2, which were of the same order of magnitude as those found for other catalysts of the Friedel–Crafts type in homogeneous systems. The temperature (30° for zinc chloride, 0–40° for sulfuric acid) and solvent (ether for boron fluoride and zinc chloride, nitrobenzene for sulfuric acid) do not allow direct comparison with the other experiments.

Theories have been proposed in which the catalyst is intimately associated with all stages of polymerization.[6] It is suggested here that the varying r_1 and r_2 found are characteristic, not of a free carbonium ion, but of such an ion modified by the proximity of the catalyst.

With all the catalysts, 3,4-dichlorostyrene appears to be relatively more reactive than the 2,5-isomer, for which $r_1 = 14.8$, $r_2 = 0.34$.[3]

(6) (a) C. M. Fontana and G. A. Kidder, THIS JOURNAL, **70**, 3745 (1948); (b) F. R. Mayo and C. Walling, *ibid.*, **71**, 3845 (1949).

LINCOLN 8, NEBR. RECEIVED SEPTEMBER 23, 1950

Methylation of 5-Phenyltetrazole

BY RONALD A. HENRY

From the reaction of equivalent quantities of methyl iodide and 5-phenyltetrazole in alkaline solution Elpern and Nachod[1] isolated in 56% yield a product which they considered to be 2-methyl-5-phenyltetrazole since its melting point (41.9–46.9°) differed from that of the previously known 1-methyl-5-phenyltetrazole[2] (m.p. 103–104°). Although the melting point range for their product was very broad, they did not report any attempts either to improve its purity, or to detect the 1-methyl isomer which might have been formed simultaneously in the methylation.

A somewhat similar situation exists in some work by Mihina and Herbst,[3] who studied the reaction of potassium 5-phenyltetrazole with *p*-nitrobenzyl bromide and benzyl bromide. Although these latter authors stated that the structures of their products were not unequivocally established, their results seemed to indicate preferential alkylation at the 2-position on the ring.

We have found, however, that the methylation of 5-phenyltetrazole in alkaline solution consistently yields two isomeric compounds which can be separated by careful fractional crystallization. One of these, obtained in about 20% yield, is identical with 1-methyl-5-phenyltetrazole; the other isomer is formed in about 80% yield and, when free of the 1-methyl derivative, melts sharply at 50.5–51°. These results indicate that methylation does occur predominantly, but not exclusively, on the 2-position.

(1) B. Elpern and F. C. Nachod, THIS JOURNAL, **72**, 3379 (1950).

(2) J. von Braun and W. Rudolph, *Ber.*, **74**, 267 (1941); also E. K. Harvill, R. M. Herbst, E. C. Schreiner and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(3) J. S. Mihina and R. M. Herbst, *ibid.*, **15**, 1082 (1950).

Experimental[4]

2-Methyl-5-phenyltetrazole and 1-Methyl-5-phenyltetrazole.—A solution of 8.25 g. of methyl iodide (0.058 mole) in 95 ml. of acetone was added to a cold solution of 8.3 g. of 5-phenyltetrazole (0.057 mole) and 4.65 g. of sodium hydroxide (0.116 mole) in 23 ml. of water. The mixture was refluxed for two hours; at the end of one hour an additional 8.25 g. of methyl iodide was added to make up for losses due to evaporation. The solution was cooled, mixed with 100 ml. of benzene, and washed with water until the washings were no longer alkaline. After the benzene layer had been dried over calcium chloride, the solvent was evaporated to yield 9.1 g. (quantitative) of soft, yellow crystalline material; m.p. 41–46°.

The mixture of isomers was dissolved in 75 ml. of diethyl ether and 10 ml. of benzene, filtered, and the filtrate treated with 25 ml. of petroleum ether (Skellysolve B). Overnight cooling at 0° yielded 1.34 g. of colorless needles, m.p. 103–104°. A mixed melting point with an authentic sample of 1-methyl-5-phenyltetrazole[2] was 103–104°. Addition of more petroleum ether to a permanent turbidity and chilling gave 0.45 g. more of this same isomer, m.p. 101–103°. The total yield amounted to 19.7% of theory.

The 2-methyl-5-phenyltetrazole was recovered by evaporating the mother liquors to about 40 ml., decolorizing with Norite A, filtering, and chilling the filtrate. Long, coarse needles and prisms crystallized slowly; the first crop weighed 2.55 g. and melted at 50°. Additional, less pure, material could be obtained by evaporating the filtrate to dryness; the total recovery was about 80% of theory. One recrystallization from Skellysolve B raised the melting point to 50.5–51°.

Anal. Calcd. for $C_8H_8N_4$: C, 59.93; H, 5.04; N, 34.98. Found: C, 60.10; H, 5.13; N, 35.27.

(4) All melting points are corrected.

INORGANIC CHEMISTRY BRANCH
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Some New Pentavalent Salts of Triarylbismuth Compounds[1]

BY HENRY GILMAN AND HARRY L. YALE[2]

Pentavalent bismuth salts of the general formula $R_3Bi(O_2CR')_2$ have been prepared by two procedures[3]

$$R_3BiCO_3 + 2R'CO_2H \longrightarrow R_3Bi(O_2CR')_2 + CO_2 + H_2O \quad (1)$$

$$R_3BiCl_2 + 2R'CO_2M \longrightarrow R_3Bi(O_2CR')_2 + 2MCl\ (M = Ag \text{ or } Na) \quad (2)$$

The first method was of more general application.

While some of these pentavalent derivatives possessed potential water solubilizing groups, all attempts to prepare appropriate salts resulted in complete dissociation.

These pentavalent compounds crystallized from benzene or acetone with one or two molecules of solvent of crystallization. With some compounds, these transparent crystals, on heating, gave the powdery solvent-free product; with others, more profound decomposition to tarry products occurred.

The new pentavalent derivatives are listed in Table I.

(1) For the preceding paper in the series on organobismuth compounds, see H. Gilman and H. L. Yale, THIS JOURNAL, **72**, 8 (1950).

(2) E. R. Squibb and Sons, New Brunswick, N. J.

(3) Both procedures have been utilized by the earlier workers in the field; see H. Gilman and H. L. Yale, *Chem. Revs.*, **30**, 281 (1942), for a survey of the literature.

TABLE I

PENTAVALENT SALTS OF TRIARYLBISMUTH COMPOUNDS

No.	Compound	Procedure	Recrystn. solvent	Yield, %	M.p., °C. (uncor.) (dec.)	Bismuth, % Calcd.	Found
1	$(C_6H_5)_3Bi(O_2CC_6H_4OH\text{-}o)_2$	2	C_6H_6–petr. ether	52.0	184–185	29.26	29.35, 29.37
2	$(C_6H_5)_3Bi(O_2CC_6H_4OH\text{-}p)_2$[a]	1	Acetone	81.6	250	29.26	29.04
3	$(C_6H_5)_3Bi(O_2CC_6H_4NH_2\text{-}o)_2\cdot C_6H_6$[b]	1	C_6H_6	90.2	95–96	26.51	27.00
4	$(C_6H_5)_3Bi(O_2CC_6H_4NH_2\text{-}p)_2\cdot 2(CH_3)_2CO$	1	Acetone	69.8	148	25.24	25.34
5	$(C_6H_5)_3Bi(O_2CC_6H_4NH_2\text{-}p)_2$[c]	..	.....	..	148	29.33	29.23
6	$(C_6H_5)_3Bi(O_2CCH{=}CHC_6H_5)_2$	2	$CHCl_3$–CH_3OH	50.0	176–178	28.47	28.66
7	$(C_6H_5)_3Bi(O_2CC_6H_4CO_2H\text{-}o)_2$	1	$CHCl_3$–petr. ether	63.3	168–169	27.14	27.00, 27.13
8	$(C_6H_5)_3Bi{-}O_2CC_6H_4CO_2\text{-}o$	2	Aq. alc.	58.3	155–165	34.60	34.87, 34.73
9	$(C_6H_5)_3Bi(O_2CCH_2Cl)_2$	1	Acetone	96.5	155–156	33.33	33.41
10	$(C_6H_5)_3Bi(SC_6H_5)_2$	2	Aq. alc.	35.0	44	31.75	31.44
11	$(p\text{-}CH_3C_6H_4)_3Bi(O_2CC_6H_4OH\text{-}o)_2\cdot C_6H_6$	2	C_6H_6	65.5	164–165	24.99	25.20, 25.52
12	$(p\text{-}CH_3C_6H_4)_3Bi(O_2CC_6H_4OH\text{-}o)_2$	..	.....	..	164–165	27.56	27.49, 27.95
13	$(p\text{-}CH_3C_6H_4)_3Bi(O_2CC_6H_5)_2$	2	$CHCl_3$–CH_3OH	69.0	168–169	28.85	28.66, 29.02
14	$(o\text{-}CH_3C_6H_4)_3Bi(O_2CC_6H_4OH\text{-}o)_2\cdot C_6H_6$[b]	2	C_6H_6	51.0	150–151	25.01	24.99
15	$(p\text{-}ClC_6H_4)_3Bi(O_2CC_6H_4OH\text{-}o)_2$	2	C_6H_6–petr. ether	85.7	187	25.56	26.00, 26.02

[a] Crystallized with acetone of crystallization. Before analysis, the sample was freed of acetone by drying 4 hr. at 95°. [b] Decomposed when attempt was made to free solvent of crystallization. [c] Obtained from solvated compound.

Experimental Part

Procedures 1 and 2 will be illustrated in the examples:

Triphenylbismuth Dianthranilate.—To a boiling solution of 1.0 g. of anthranilic acid in 10.0 ml. of acetone was added 1.3 g. (0.0026 mole) of triphenylbismuth carbonate. Gas was evolved. The mixture was refluxed one-half hour, cooled and diluted with 10.0 ml. of water. The precipitated solid was filtered, dried and recrystallized from benzene.

Tri-*p*-tolylbismuth Disalicylate.—A mixture of 2.1 g. (0.004 mole) of tri-*p*-tolylbismuth dichloride, 1.5 g. of sodium salicylate and 50 ml. of dioxane was shaken 36 hours at room temperature, diluted with 50 cc. of water and the precipitated solid isolated and purified as above.

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The Effect of Competitive Inhibitors on the Milk Clotting Activity of α-Chymotrypsin[1]

BY H. T. HUANG AND CARL NIEMANN[2]

Independent investigations conducted during the past two years[3-5] have provided considerable support for the idea that α-chymotrypsin possesses but one catalytically active site per molecule, and it is now clear that α-chymotrypsin activity can be observed, with selected synthetic substrates, from *p*H 5.5, for L-phenylalanine ethyl ester,[6] to *p*H 8.5, for an acylated-L-tryptophanamide.[7] Furthermore there is evidence[3] that the milk clotting activity of α-chymotrypsin, commonly evaluated at approximately *p*H 5, is associated with the same catalytically active site that is responsible for the hydrolysis of the synthetic specific substrates.

It follows from the above observations that synthetic, low molecular weight, competitive inhibitors of the α-chymotrypsin-catalyzed hydrolysis of synthetic specific substrates, at *p*H 7.9, might be expected to exhibit their inhibitory properties in the α-chymotrypsin-catalyzed milk clotting process if their respective enzyme-inhibitor dissociation constants are not greatly influenced by changes in *p*H. It is clear that the effects associated with *p*H dependencies of modest magnitude can be minimized by evaluating the relative effectiveness of two uncharged and structurally similar competitive inhibitors. Therefore, the inhibitory properties of two such inhibitors of α-chymotrypsin, whose enzyme-inhibitor dissociation constants were previously evaluated at 25° and *p*H 7.9, were tested in respect to their influence upon the milk clotting activity of this enzyme at 25° and *p*H 4.8.

It will be seen from the data given in Table I that the two inhibitors, acetyl-D-tryptophanamide and acetyl-D-tryptophan methyl ester, cause a definite increase in the clotting time over that observed with the control, and while it is doubtful that the results obtained in these experiments are other than qualitative it is of interest to note that the ester is approximately twenty times as active as an inhibitor in the clotting process at *p*H 4.8 than is the amide, a ratio which is roughly the order expected on the basis of their respective K_I values at 25° and *p*H 7.9, *i.e.*, acetyl-D-tryptophan methyl ester, 0.089×10^{-3} *M*[8]; acetyl-D-tryptophanamide, 2.7×10^{-3} *M*,[7] and a similar enzyme-inhibitor dissociation constant *p*H dependency.

TABLE I

INHIBITION OF THE MILK-CLOTTING ACTIVITY OF α-CHYMOTRYPSIN BY TWO REPRESENTATIVE COMPETITIVE INHIBITORS[a]

System	Clotting time in seconds[b] Series A	Series B
No added inhibitor	146 (2.0)	166 (1.7)
With inhibitor I[c]	176 (2.0)	188 (1.5)
With inhibitor II[d]	171 (2.9)	189 (2.6)

[a] Two typical examples from a series of experiments performed at 25° and *p*H 4.8. [b] With indicated standard error based upon a minimum of five separate observations. [c] 2.86×10^{-3} *M* in acetyl-D-tryptophanamide. [d] 0.14×10^{-3} *M* in acetyl-D-tryptophan methyl ester.

(1) Supported in part by a grant from Eli Lilly and Co.

(2) To whom inquiries regarding this article should be addressed.

(3) E. F. Jansen, M. D. Fellows-Nutting, R. Jang and A. K. Balls, *J. Biol. Chem.*, **185**, 209 (1950).

(4) R. J. Foster and C. Niemann, THIS JOURNAL, **73**, 1552 (1951).

(5) H. T. Huang and C. Niemann, *ibid.*, **73**, 1555 (1951).

(6) H. and V. Goldberg, *Arch. Biochem.*, **29**, 154 (1950).

(7) H. T. Huang and C. Niemann, THIS JOURNAL, **73**, 1541 (1951).

(8) H. T. Huang and C. Niemann, *ibid.*, **73**, 3228 (1951).