TABLE I

NITRATION OF SUBSTITUTED MALONIC ESTERS, $R{-}\overset{NO_2}{C}(CO_2C_2H_5)_2$

R	Yield	B.p. °C.	Pressure	$n^{25}D$	Analyses,[a] % Calcd. C	H	N	Found C	H	N
Isopropyl	60	83–84	0.3 mm.	1.4337	48.6	6.89	5.67	47.06	6.76	5.58
Isobutyl	78	88–89	0.5 mm.	1.4351	50.6	7.29	5.37	51.43	7.35	5.04
n-Butyl	75	93–94	0.5 mm.	1.4340	50.6	7.29	5.37	50.03	7.48	5.11
Cyclohexyl	15	110–120	5μ	1.4597	54.4	7.31	4.88	54.47	7.42	4.73
n-Decyl	97[b]	120–130	14μ	1.4450	59.2	9.05	4.06	59.38	9.30	4.56

[a] Analysis by the Elek Microanalytical Laboratories, Los Angeles, Calif. [b] Yield based on total weight recovered.

hour at 60° then cooled and poured onto 200 g. of chipped ice. After the ice had melted the oily layer was extracted with ether, and washed with 5% sodium bicarbonate solution until neutral, then with water. After drying, the ether was removed by distillation and the remaining liquid distilled through a small Vigreux column. The diethyl alkylnitromalonates were obtained as colorless oily liquids.

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Reaction of Tyrosine with Formaldehyde in Acid Solution

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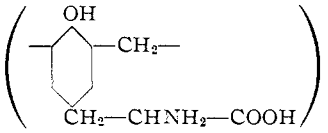
In a study of protein reactions,[1] we wished to have available, as one type of model, a non-dialyzable substance containing a number of free amino groups. It occurred to us that tyrosine should react with formaldehyde in acid solution[2] to form such a polymer. The authors of the only previous studies on this system[3,4] believed that they had obtained isoquinoline derivatives. We have prepared products by the methods they described and also under other reaction conditions and find that they are not isoquinoline derivatives but that instead they display the properties to be expected of acid-catalyzed tyrosine–formaldehyde polymers.

The preparations were soluble in dilute acid and alkali but insoluble in the neutral range. Depending upon the conditions used in the polymerization, 40–70% was retained in dialyzing bags (Visking tubing) after extensive dialysis. Free amino nitrogen (by Van Slyke) was equivalent to 75–93% of the total nitrogen. These observations, together with the known reactions of other substituted phenols with formaldehyde,[5] indicate that the polymer is composed for the most part of units with the structure



The low total nitrogen and amino nitrogen analyses in all likelihood reflect the presence of additional methylol groups and methylene cross-links involving amino nitrogen in parts of the polymer.

Experimental

Preparation.—Tyrosine (20 g., 0.11 mole) was dissolved in 12.7 *N* sulfuric acid (17.5 ml., 0.11 mole) and to the solution, which rapidly solidified, was added formalin (40% formaldehyde, 8.4 ml., 0.11 mole). This mixture was autoclaved at 20 lb. pressure for 17 hours,[6] dissolved in water and thoroughly dialyzed.[7] The product tended to precipitate in the dialyzing bag but could be redissolved by dialyzing for a short time against dilute sodium carbonate solution. The final solution contained 48% of the original nitrogen (by Kjeldahl). The product was precipitated by the addition of dilute sulfuric acid to *p*H 4.1, washed with water, alcohol and ether, and air-dried at room temperature. It contained 12.2% water.

Anal. Calcd. for $C_{10}H_{11}O_3N$: N, 7.2; amino N, 7.2. Found (dry basis): N, 6.8; amino N, 5.4.

A product prepared according to Wellisch[4] with methylal and concentrated hydrochloric acid was 44% retained by extensive dialysis. The amino nitrogen content of the final product amounted to 70% of the total nitrogen.

Found (dry basis): N, 6.8; amino N, 4.8.

Properties.—The polymer gave a strong positive ninhydrin test, but quantitatively[8] the color was approximately only 70% of that to be expected from the Van Slyke amino nitrogen analyses (15-minutes reaction period). Strong color tests were also given by the Folin color reagent for free phenolic groups.[9] The product was not attacked by tyrosine decarboxylase (from *S. faecalis*), nor did it inhibit the rate of decarboxylation of tyrosine by tyrosinase. Its reaction with neutral 30% glucose solution was described previously.[1]

Acknowledgment.—The tyrosinase tests were performed by B. E. Axelrod with a preparation furnished by J. C. Lewis.

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(1) A. Mohammad, H. Fraenkel-Conrat and H. S. Olcott, *Arch. Biochem.*, **24**, 157 (1949).

(2) The polymer formed from tyrosine and formaldehyde in alkaline solution has been described by A. E. Brown, THIS JOURNAL, **68**, 1011 (1946). It contains no free amino nitrogen.

(3) A. Pictet and T. Spengler, *Ber.*, **44**, 2030 (1911).

(4) J. Wellisch, *Biochem. Z.*, **49**, 173 (1913).

(5) Reviewed in J. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1953.

(6) The polymerization probably does not require this extended reaction time. A somewhat similar product was obtained after 4 hours of autoclaving.

(7) Provision should be made for the considerable increase in volume which occurs.

(8) V. J. Harding and R. M. MacLean, *J. Biol. Chem.*, **24**, 503 (1916).

(9) R. M. Herriott, *J. Gen. Physiol.*, **19**, 283 (1935).

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The Pyridylethylation of Active Hydrogen Compounds. IV. The Acid-catalyzed Pyridylethylation of Primary Amines

BY HENRY E. REICH[1] AND ROBERT LEVINE

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In previous papers from this Laboratory the pyridylethylation of ketones[2,3] and of secondary amines[4] was discussed.

The present report is concerned with the con-

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(1) American Cyanamid Company Research Fellow, 1952–1954.

(2) R. Levine and M. H. Wilt, THIS JOURNAL, **74**, 342 (1952).

(3) M. H. Wilt and R. Levine, *ibid.*, **75**, 1368 (1953).

(4) H. E. Reich and R. Levine, *ibid.*, **77**, 4913 (1955).