TABLE I

NITRATION OF SUBSTITUTED MALONIC ESTERS, $R—C(CO_2C_2H_5)_2$

R	Yield	B.p. °C.	Pressure	$n^{25}D$	Analyses,[a] % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found 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.

AEROJET-GENERAL CORPORATION
AZUSA, CALIFORNIA

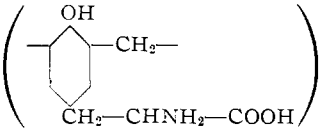
Reaction of Tyrosine with Formaldehyde in Acid Solution

BY HAROLD S. OLCOTT

RECEIVED MAY 31, 1955

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.

(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.

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.

(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).

WESTERN UTILIZATION RESEARCH BRANCH
AGRICULTURAL RESEARCH SERVICE
U. S. DEPARTMENT OF AGRICULTURE
ALBANY 10, CALIFORNIA

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

BY HENRY E. REICH[1] AND ROBERT LEVINE

RECEIVED MAY 19, 1955

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-

(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).

densation of 2-vinylpyridine with primary amines. Although other workers[5a,b] and we[4] have been able to condense 2-vinylpyridine with morpholine and piperidine in high yields under non-catalytic conditions, attempts in the present study to pyridylethylate aniline under non-catalytic conditions failed.

However, when a methanol solution of one equivalent each of aniline, 2-vinylpyridine and glacial acetic acid was refluxed for eight hours, a 78% yield of a monopyridylethylated product (b.p. 167–168° at 2.5 mm., m.p. 40.6–41.5°) was obtained. During the course of this study, Clifford[6] was issued a patent in which it is claimed that when a mixture of equivalents of aniline and 2-vinylpyridine and catalytic amounts of acetic acid and copper(II) acetate is refluxed for ten hours and then distilled, there is obtained a pyridylethylated aniline (b.p. 175° at 2 mm., m.p. 141–143°). Using the experimental conditions described in the patent, we have obtained a 60–64% yield of a pyridylethylated product (b.p. 167–168° at 2.5 mm., m.p. 40.6–41.5°). Furthermore, since the material prepared by both the Clifford method and our method is identical as shown by taking mixed melting points between the compounds themselves as well as their picrates, the melting point reported in the patent is in error.

Although by analogy with our work on secondary amines[4] there seems to be little doubt that the aniline-2-vinylpyridine adduct is 2-(2-anilinoethyl)-pyridine (I), it was desirable to prove this unequivocally. To obtain an authentic sample of I, ethyl 2-pyridylacetate[7] was aminolyzed by aniline in 65% yield to give 2-pyridylacetanilide. However, attempts to reduce this anilide either catalytically or by lithium aluminum hydride failed. Attempts to prepare an authentic sample of I by a Mannich reaction between 2-picoline, formaldehyde and aniline hydrochloride were also unsuccessful.

Therefore, the structure of I was established indirectly by alkylating it with methyl iodide in 67% yield to give 2-(2-N-methylanilinoethyl)-pyridine (II). The tertiary amine II was obtained previously by the pyridylethylation of N-methylaniline[4] and its structure was established by comparison with an authentic sample which was prepared by the reduction of N-methyl-2-pyridylacetanilide

$$2\text{-}C_5H_4NCH{=}CH_2 + C_6H_5NH_2 \xrightarrow[CH_3OH]{CH_3CO_2H,}$$

$$2\text{-}C_5H_4NCH_2CH_2NHC_6H_5 \xrightarrow[2,\ CH_3I]{1,\ C_6H_5Li}$$

$$2\text{-}C_5H_4NCH_2CH_2N(CH_3)C_6H_5$$

II

Although a number of attempts to pyridylethylate 2-aminopyridine under acidic conditions failed, several other primary amines (Table I) have been condensed with 2-vinylpyridine in good yields. It is interesting to note that attempts to condense 2-

TABLE I

AMINES OF THE TYPE  CH_2CH_2NHR

Amine pyridylethyated	Catalyst	(Mole)	Yield, %	M.p., or b.p., °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	M.p., °C.	Formula	Picrated Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Hydroxyl-[a]	HCl[b]		75	105.9–106.8[g]		$C_7H_{10}N_2O$	20.29	20.09	169–170.2	$C_{13}H_{13}N_5O_8$					19.07	19.14
Methyl-	HCl[b]		64	117–118	25	$C_8H_{12}N_2$	20.59	20.50	193.8–195.2	$C_{20}H_{18}N_8O_{14}$[c]	40.40	40.65	3.03	3.32	18.86	19.26
Ethyl-	HCl[b]		52	109–110	12	$C_9H_{14}N_2$	18.67	18.96	148.4–149.8	$C_{21}H_{20}N_8O_{14}$[d]	41.45	41.71	3.29	3.32	18.42	18.77
n-Propyl-	HOAc	(1.0)	49	78–80	1	$C_{10}H_{16}N_2$	17.07	17.41	158–159	$C_{22}H_{22}N_8O_{14}$[c]	42.44	42.70	3.54	3.41	18.01	18.37
n-Butyl-	HOAc	(1.0)	57	132–133	12	$C_{11}H_{18}N_2$	15.73	15.97	144.6–146.2	$C_{23}H_{24}N_8O_{14}$[c]	43.40	43.60	3.77	3.68	17.61	17.84
i-Butyl-	HOAc	(1.0)	55	85–87	1.5	$C_{11}H_{18}N_2$	15.73	15.97	158.6–159.4	$C_{23}H_{24}N_8O_{14}$[d]	43.40	43.54	3.77	3.33	17.61	17.83
Aniline	HOAc	(1.0)	78	167–168	2.5	$C_{13}H_{14}N_2$	14.14	13.88	169.5–170.5	$C_{19}H_{17}N_5O_7$					16.39	16.45
	HOAc	(0.2)	75	40.6–41.5[e]												
Benzyl-	HOAc	(1.0)	67	140–141	1.7	$C_{14}H_{16}N_2$	13.21	13.35	163–164.2	$C_{20}H_{19}N_5O_7$					15.87	15.97
2-Furfuryl-	HOAc	(1.0)	80	120–121	1	$C_{12}H_{14}N_2O$	13.86	13.84	163–164.5	$C_{18}H_{17}N_5O_8$					16.24	16.15
2-Thenyl-[f]	HOAc	(1.0)	74	144–146	1.7	$C_{12}H_{14}N_2S$	12.84	13.00	168.6–169.6	$C_{18}H_{17}N_5O_7S$					15.67	15.89
Cyclohexyl-	HOAc	(0.2)	60	134–135	1.5	$C_{13}H_{20}N_2$	13.73	13.91	138–139.8	$C_{19}H_{23}N_5O_7$					16.17	15.97
	HOAc	(1.0)	43													

[a] Molar ratio of amine to 2-vinylpyridine, 0.7. [b] The primary amine was used as its hydrochloride. [c] Recrystallized from 60–70° petroleum ether. [d] All picrates were recrystallized from 95% ethanol. [e] Dipicrate, other picrates are monopicrates. [f] Molar ratio of amine to 2-vinylpyridine, 0.83.

(5a) W. E. Doering and R. A. N. Weil, THIS JOURNAL, **69**, 2461 (1947).

(5b) A. H. Sommers, M. Freifelder, H. B. Wright and A. W. Weston, *ibid.*, **75**, 57 (1953).

(6) A. M. Clifford, U. S. Patent 2,615,982 (October 28, 1952).

(7) N. N. Goldberg, B. M. Perfetti and R. Levine, THIS JOURNAL, **75**, 3843 (1953).

aminopyridine with acrylonitrile, a non-cyclic analog of 2-vinylpyridine, also have failed.[8]

It should be noted that while cyclohexylamine was pyridylethylated in 60% yield under acidic conditions, the same reaction failed when it was attempted earlier[5] under non-catalytic conditions.

The mechanism for the acid-catalyzed pyridylethylation of primary amines is probably the same as that suggested earlier[4] for the analogous reactions with secondary amines.

Experimental

Reaction of Equivalents of Aniline, 2-Vinylpyridine[9] and Acetic Acid in Methanol Solution.—A solution of aniline (85.0 g., 0.914 mole), 2-vinylpyridine (96.0 g., 0.914 mole), glacial acetic acid (54.8 g., 0.914 mole) and 250 ml. of absolute methanol was refluxed for eight hours, allowed to cool to room temperature and then allowed to stand at room temperature for nine hours. The methanol was removed at atmospheric pressure and the reaction mixture was then poured onto ice and made strongly basic with 10% sodium hydroxide solution. The basic solution was extracted with ether, the extracts dried over anhydrous sodium sulfate, the solvent removed at atmospheric pressure and the residue distilled in vacuum to give 142 g. (78%) of 2-(2-anilinoethyl)-pyridine, b.p. 167–168° at 2.5 mm., m.p. 40.6–41.5° (from 60–70° petroleum ether). *Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.14. Found: C, 78.62; H, 6.78; N, 13.88. The amine gave a monopicrate, m.p. 169.5–170.5° (from 95% ethanol). *Anal.* Calcd. for $C_{19}H_{17}O_7N_5$: N, 16.39. Found: N, 16.45. From this reaction there were also obtained 11.0 g. of 2-vinylpyridine, b.p. 80–82° at 50 mm., 14.7 g. of aniline, b.p. 74–80° at 23 mm., and 12.0 g. of a non-distillable tarry nitrogenous residue. The procedure described above was used in all the pyridylethylations.

Reaction of Aniline with 2-Vinylpyridine Using Clifford's Procedure.—A mixture of aniline (93.0 g., 1.0 mole), 2-vinylpyridine (105 g., 1.0 mole), glacial acetic acid (4.5 g., 0.075 mole) and copper(II) acetate (0.7 g., 0.04 mole) was refluxed for ten hours and then distilled directly to give 126.0 g. (64%) of 2-(2-anilinoethyl)-pyridine, b.p. 166–168° at 2.5 mm., m.p. 40.5–41.4° (from 60–70° petroleum ether); 38.7 g. of aniline, b.p. 58° at 2 mm.; 1.0 g. of 2-vinylpyridine, b.p. 65–70° at 32 mm., and 31.0 g. of a non-distillable tarry nitrogenous residue. Mixed melting points between the pyridylethylated aniline obtained in this experiment with the material of the same melting point obtained in the preceding experiment as well as mixed melting points of their respective monopicrates showed no depression.

Preparation of 2-Pyridylacetanilide.—A solution of ethyl 2-pyridylacetate[7] (10.0 g., 0.06 mole) and aniline (7.5 g., 0.08 mole) was heated at 170° for three hours and then allowed to cool to room temperature. The solid which precipitated was filtered and recrystallized from benzene to give 8.2 g. (65%) of 2-pyridylacetanilide, m.p. 134–135°.[10]

Alkylation of 2-(2-Anilinoethyl)-pyridine with Methyl Iodide.—To an ether solution of phenyllithium, prepared from 5.6 g. (0.8 mole) of lithium ribbon, 62.8 g. (0.4 mole) of bromobenzene and 400 ml. of anhydrous ether, was added 79.2 g. (0.4 mole) of 2-(2-anilinoethyl)-pyridine, dissolved in 100 ml. of anhydrous ether followed by 56.8 g. (0.4 mole) of methyl iodide, dissolved in 100 ml. of anhydrous ether and added at such a rate that the ether refluxed gently. After the addition of the methyl iodide was completed, the reaction mixture was refluxed for one hour, poured onto ice and made strongly basic by 10% sodium hydroxide solution. The mixture was extracted with several portions of ether, the combined extracts were dried over sodium sulfate and the solvent was removed at atmospheric pressure. The residue was distilled in vacuum to give 57.7 g. (65%) of 2-(2-N-methylanilinoethyl)-pyridine, b.p. 148–151° at 3.5 mm., and 19.4 g. of a non-distillable tarry residue. The 2-(2-N-methylanilinoethyl)-pyridine formed a monopicrate, m.p. 167–167.7° alone and when mixed with a sample prepared from the material made by the pyridylethylation of N-methylaniline.[4]

CONTRIBUTION No. 951
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH 13, PENNSYLVANIA

(8) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, THIS JOURNAL, **66**, 725 (1944).

(9) The 2-vinylpyridine was supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

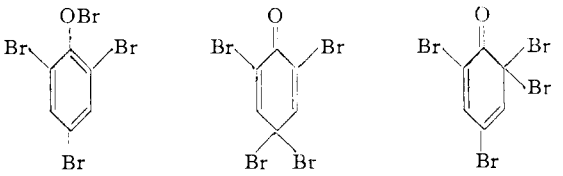
(10) F. Galinovsky and G. Kanz, *Monatsh.*, **77**, 137 (1947).

The Structure of Tribromophenol Bromide

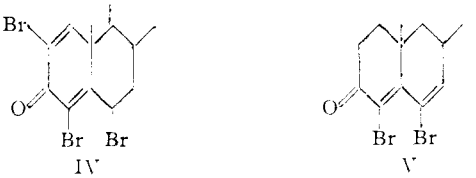
BY JOHN A. PRICE

RECEIVED MAY 28, 1955

It has not been possible to choose with confidence between the structures I[1] and II[2] for the product obtained from the further bromination of 2,4,6-tribromophenol. However, II appears to be favored by the most recent physical evidence[2c] and the results of Forman and Sears on the halogenation of 3-methyl-4,6-di-*t*-butylphenol[3] and of Coppinger and Campbell on the bromination of 2,6-di-*t*-butyl-4-methylphenol.[4]



A clear choice in favor of II can be made on the basis of its infrared spectrum, which shows a characteristic strong maximum at 5.99 μ, clearly indicative of a conjugated carbonyl. Infrared absorption at closely similar wave lengths was observed with the related cyclohexadienones studied by Forman and Sears[3] and by Coppinger and Campbell.[4] Furthermore, its ultraviolet spectrum which shows a maximum at 280 mμ, ϵ 9270,[5] allows a choice between the cross-conjugated *p*-quinonoid structure II and the *o*-quinonoid form III in favor of the former. The values show excellent correspondence with those of IV, λ_{max} 274 mμ, ϵ 10,600, and may be contrasted with those of V, λ_{max} 296, ϵ 19,400.[6]



III would be expected to absorb at even longer wave lengths than V.[7]

Experimental

Tribromophenol bromide was prepared according to Benedikt[1a] and recrystallized from chloroform, m.p. 124°

(1) (a) R. Benedikt, *Ann.*, **199**, 127 (1879); (b) W. M. Lauer, THIS JOURNAL, **48**, 442 (1926); (c) I. Ssuknewitsch and S. Budnitzkii, *J. prakt. Chem.*, **138**, 22 (1933).

(2) (a) J. Thiele and H. Eichwede, *Ber.*, **33**, 673 (1900); (b) J. H. Kastle and R. Speyer, THIS JOURNAL, **27**, 40 (1902); (c) C. H. R. Elston, A. T. Peters and F. M. Rowe, *J. Chem. Soc.*, 367 (1948).

(3) L. E. Forman and W. C. Sears, THIS JOURNAL, **76**, 4977 (1954).

(4) G. M. Coppinger and T. W. Campbell, *ibid.*, **75**, 735 (1953).

(5) Compare the spectrum of the related tribromophenol chloride examined by Elston, Peters and Rowe, ref. 2c, which has λ_{max} 275–280, ϵ 10,000.

(6) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(7) R. B. Woodward, THIS JOURNAL, **64**, 72 (1942).