TABLE I

REACTION OF METHYL α-D-GLUCOPYRANOSIDE WITH 1 MOLAR EQUIV OF 3,4-DIHYDRO-2H-PYRAN

Reaction time[a]	Glycoside converted, %	Methylated methyl α-D-glucopyranoside, yield[b]	D-Glucose ether
30 min	16	95	2,3,4-Tri-O-methyl Di-O-methyl
4 hr[c]	27		2,3,4-Tri-O-methyl (58%)[d]
4 days[c]	88	94	2,3,4-Tri-O-methyl[e] Di-O-methyl[c]

[a] Ambient temperature. [b] Calculated on the basis of the material methylated. [c] See Experimental Section. [d] Yield as per cent of the acetal mixture. [e] 5:1 ratio by gas–liquid partition chromatography.

of *p*-toluenesulfonic acid (80 mg). The reaction mixture was stirred for 4 days at ambient temperatures. Unchanged methyl α-D-glucopyranoside was removed by filtration; sodium hydrogen carbonate (100 mg) and water (2.0 ml) were added to the filtrate, which was concentrated to a syrup. The addition of diethyl ether precipitated unchanged methyl α-D-glucopyranoside. The filtrate was concentrated to a syrup to yield 18.9 g. Tlc (two ascents, solvent C) showed one major component present. Data obtained at other reaction times are shown in Table I.

Methylation of the Reaction Product.—A portion of the above syrup (15 g) was dissolved in methyl iodide (100 ml), and silver oxide (25 g) was added. The mixture was shaken overnight at room temperature (or alternatively refluxed overnight), filtered, and concentrated. The methylation procedure was repeated (4–5 times) until ir analysis of the syrup showed the hydroxyl peak to be negligible.

Hydrolysis and Analysis of the Methylated Product.—A portion (5 g) of the above methylated syrup was hydrolyzed with 2 *N* sulfuric acid for 4 hr under reflux. Paper chromatographic examination (solvent A or B) of the neutralized (barium carbonate) hydrolyzate indicated a mixture of tetra-, tri-, and di-*O*-methylglucose. The hydrolyzate (3 g) was converted into the corresponding methyl glycosides by treatment with 3% methanolic hydrogen chloride under reflux. After neutralization (silver carbonate) and filtration, the solution was concentrated and dissolved in chloroform (*c* 40). The glycosides (0.5 ml chloroform solution, 200-mg sample) were separated[8] by vpc at 225° on a 3.66 m (12 ft) preparative column of 10% neopentyl glycol succinate on acid-washed Chromosorb W, 60–100 mesh, at a helium flow of 60 ml per min. The methyl glycosides were collected in a cooling chamber on elution from the gas chromatograph and weighed on a microbalance. The ratio of tri- to di-*O*-methyl glucoside was 5:1 (total return 75%). Hydrolysis (2 *N* sulfuric acid, 4 hr reflux) of the tri-*O*-methylglucosidic fraction liberated a tri-*O*-methyl-D-glucose, identified as 2,3,4-tri-*O*-methyl-D-glucose, $[\alpha]^{22}D$ +71° (*c* 1.0, acetone) (lit.[9] $[\alpha]^{22}D$ +70.5°). The syrup showed R_{glpc} values 0.87 (solvent A, lit.[10] R_{glpc} 0.85) and 0.73 (solvent B), identical with those shown by an authentic specimen.[11] Electrophoresis in borate buffer, pH 10, for 5 hr at 600 V showed the sugar to have M_{glpc} 0 (lit.[12] M_{glpc} 0) as did the authentic specimen.

The di-*O*-methyl-D-glucose fraction was not investigated. The tetra-*O*-methyl-D-glucose fraction was negligible in amount.

Prepartion of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside (3).—Methyl α-D-glucopyranoside (10 g) was dissolved in dry *N*,*N*-dimethylformamide (250 ml). To this solution was added 3,4-dihydro-2*H*-pyran (5.0 g, 1:1.1 molar ratio) and *p*-toluenesulfonic acid (0.1 g). The mixture was stirred in a closed flask for 3 hr at room temperature. The acid was neutralized with aqueous ammonia. The syrup obtained on removal of *N*,*N*-dimethylformamide, under reduced pressure, was thoroughly mixed with chloroform and unchanged methyl α-D-glucopyranoside separated. The chloroform solution was concentrated to a syrup (3.8 g) which showed one major spot along with several minor spots by tlc (solvent D). The major reaction product was isolated as a syrup by preparative tlc to yield 2.2 g. A portion (25%) of this syrup (probably a mixture of diastereoisomers) crystallized with difficulty from ethyl acetate: mp 170°; $[\alpha]^{20}D$ +40° (*c* 1.0, chloroform); X-ray powder diffraction data 13.81 s (**3**), 7.29 m, 6.75 m, 6.13 w, 5.62 vs (1), 5.27 vs (2), 4.54 s, 4.09 m, 3.97 m, 3.74 m, 3.47 w, 3.28 vw, 3.19 w, 3.03 s, 2.89 w, 2.83 w, 2.69 w, 2.50 m, 2.43 w, 2.35 w, 2.29 w.

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.91. Found: C, 52.10; H, 7.72.

Conversion of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside into *N*-Phenyl-2,3,4-tri-*O*-methyl-β-D-glucopyranosylamine.—Methyl 6-*O*-tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside (**3**, syrup, 2 g) was dissolved in methyl iodide (10 ml), and silver oxide (10 g) was added. The mixture was shaken for 24 hr at room temperature (or alternatively refluxed for the same time), filtered, and concentrated to a syrup. The methylation procedure was repeated (two–three times) until the resulting syrup showed no hydroxyl absorption in its ir spectrum. The methylated product was hydrolyzed with 1 *N* sulfuric acid for 10 hr under reflux. The evaporation of the neutralized (barium carbonate) solution afforded a syrup (1.8 g) which was homogeneous by paper chromatography (solvent A). A portion (200 mg) of the above syrup was dissolved in methanol (10 ml) followed by the addition of freshly distilled aniline (100 mg) and refluxed for 3 hr. On evaporation the product crystallized and was recrystallized from methanol to yield 150 mg, mp 145–146° undepressed on admixture with authentic[13] 2,3,4-tri-*O*-methyl-*N*-phenyl-β-D-glucopyranosylamine. The X-ray powder diffraction data[14] were identical with those of a known specimen, $[\alpha]^{20}D$ −100° (*c* 1.0, ethanol) (lit.[15] $[\alpha]^{20}D$ −103°).

Preparation of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside from Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside.—Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[16] (200 mg) was dissolved in diethyl ether (10 ml) to which *p*-toluenesulfonic acid (10 mg) and 3,4-dihydro-2*H*-pyran (0.5 ml, 1:1 molar ratio) were added. The mixture was stirred for 30 min, and the completion of the reaction was indicated by tlc (solvent D). After being neutralized with sodium carbonate and filtered, the filtrate was concentrated to a syrup and dried. This syrup (210 mg) was dissolved in anhydrous methanol (10 ml) to which was added 0.5 *N* sodium methoxide solution (1 ml). The mixture was kept at room temperature for 45 min with occasional shaking. After being treated with Amberlite 1R-120 (H^+), the methanolic solution was concentrated to a syrup which was chromatographically (thin layer, solvent D) identical with that of the major reaction product obtained by reacting methyl α-D-glucopyranoside with 3,4-dihydro-2*H*-pyran as described above.

Registry No.—**1**, 3411-23-2; **2**, 110-87-2; **3**, 17448-06-5.

(8) H. Alfes, C. T. Bishop, and F. Blank, *Can. J. Chem.*, **41**, 2621 (1963).
(9) F. Smith and R. Montgomery, "The Chemistry of Plant Gums and Mucilages," Reinhold Publishing Corp., New York, N. Y., 1959, p 533.
(10) Reference 9, p 226.
(11) For which we are indebted to Professor B. Lindberg of Stockholm.
(12) A. B. Foster, *Advan. Carbohyd. Chem.*, **12**, 93 (1957).
(13) Obtained through the courtesy of S. Kirkwood, University of Minnesota, St. Paul, Minn.
(14) M. L. Wolfrom, A. Thompson, and A. M. Brownstein, *J. Amer. Chem. Soc.*, **80**, 2015 (1958).
(15) J. D. Geerdes, B. A. Lewis, and F. Smith, *ibid.*, **79**, 4209 (1957).
(16) B. Helferich, H. Bredereck, and A. Schneidmüller, *Ann.*, **458**, 111 (1927).

The Synthesis of 5-Phenyl-3-(substituted anilino)-2(5H)-furanones in Aqueous Solution

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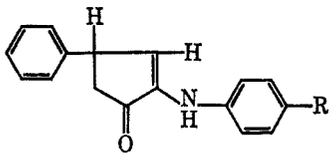
Received May 14, 1968

Condensation of substituted benzylidenepyruvic acids with substituted anilines in refluxing ethanol has been established to yield the corresponding 5-phenyl-

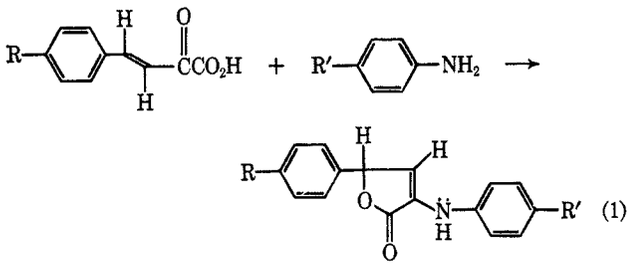
TABLE I

ELEMENTAL ANALYSES FOR A SERIES OF SUBSTITUTED 5-PHENYL-3-ANILINO-2(5H)-FURANONES.



				Calcd, %					Found, %				
No.	R	Mp, °C	Formula	C	H	O	N	X	C	H	O	N	X
I	H	164–165[a]	$C_{16}H_{13}O_2N$	76.48	5.21	12.73	5.57		76.64	5.25	12.81	5.78	
II	*p*-CO_2H	205[b]	$C_{17}H_{13}O_4N$	69.14	4.43	21.67	4.74		69.36	4.44	21.56	4.62	
III	*p*-C-CH_3 (‖ O)	174.5	$C_{18}H_{15}O_3N$	73.70	5.15	16.36	4.77		73.69	5.21	16.43	4.97	
IV	*p*-Br	157–158	$C_{16}H_{12}O_2NBr$	58.20	3.66	9.69	4.24	24.20	58.08	3.44	9.83	4.37	24.41
V	*p*-Cl	158–160	$C_{16}H_{12}O_2NCl$	67.26	4.23	11.20	4.90	12.41	67.33	4.30	11.30	4.82	12.51
VI	*p*-I	156–158	$C_{16}H_{12}O_2NI$	50.94	3.20	8.48	3.71	33.65	50.74	3.19	8.41	3.64	33.89
VII	*p*-NO_2	192–193[c]	$C_{16}H_{12}O_4N_2$	64.86	4.08	21.60	9.45		64.72	3.95	21.76	9.62	
VIII	*m*-Cl	123–124	$C_{16}H_{12}O_2NCl$	67.26	4.23	11.20	4.90	12.41	67.25	4.32	11.18	4.89	12.24
IX	*m*-Br	132–133.5	$C_{16}H_{12}O_2NBr$	58.20	3.66	9.69	4.24	24.20	58.04	3.74	9.89	4.18	24.40

[a] Lit.[2] mp 160–160.5°. [b] S. Bodforss [*Ann.*, **455**, 41 (1927)] reported mp 205° (assigned structure is incorrect this reference). [c] Lit.[2] mp 181°.



3-anilino-2(5H)-furanones[1] (eq 1), although the structure of these products was misassigned for several years.[2] We now wish to report the synthesis of several novel compounds of this class through a direct condensation reaction in aqueous solution together with some aspects of the kinetic behavior of these reactions.

Incubation of benzylidenepyruvic acid with a variety of anilines under mildly acidic conditions in aqueous solution near 80° results in the deposition of crystalline materials within a few hours or a few days depending on the nature of the aniline employed. Isolation of the crystalline species and spectroscopic investigation reveal them to be the corresponding enamine lactones (eq 1). The properties of a series of nine such compounds are collected in Tables I and II. The observed yields were greater than 80%.

In two cases, the reactions between benzylidenepyruvic acid and aniline or *p*-aminobenzoic acid, the kinetics of enamine lactone formation have been investigated in aqueous solution in the pH range 0.57–2.12, ionic strength 0.5, and at a temperature of 50°. These reactions were followed by monitoring the disappearance of benzylidenepyruvic acid polarographically. The kinetic behavior of these reactions is characterized by the following features. First, the reaction with excess aniline exhibited excellent first-order behavior following an initial loss of acid (*ca.* 10% of the total) which is increasingly rapid at more acidic values of pH. The reaction with excess *p*-aminobenzoic at pH 0.57 also exhibited an initial rapid loss of acid, which was most important at high concentrations of the amine, followed by good first-order behavior. At this pH, the reaction with aniline is first order throughout since the initial reaction is too fast to follow. It seems likely that these breaks are the consequence of the reversible attack of amine on the unsaturated linkage of the acid.[3] Second, the reaction of benzylidenepyruvic acid with aniline is first order in aniline concentration: the second-order rate constant based on total aniline concentration at 50° is 3.2×10^{-5} M^{-1} sec^{-1}. Third, the rate of the reaction of benzylidenepyruvic acid with aniline is substantially independent of the concentration of the solvated proton over the pH range investigated. Fourth, the reaction with *p*-aminobenzoic acid is more rapid than that with aniline: first-order rate constants for these reactions with 0.0625 M amine at pH 0.57 at 50° are 8.7×10^{-5} and 2×10^{-6} sec^{-1}, respectively. Qualitatively, it has been observed that the reactions with even less basic amines, such as *p*-nitroaniline, are even more rapid.

These results are reasonably accommodated by a reaction pathway involving the rapid and reversible for-

TABLE II

INFRARED AND ULTRAVIOLET SPECTRAL DATA FOR A SERIES OF SUBSTITUTED 5-PHENYL-3-ANILINO-2(5H)-FURANONES

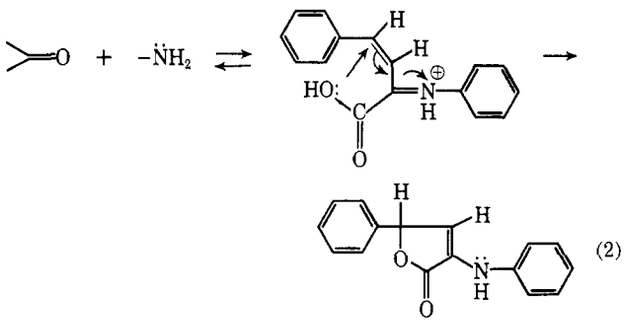
No.	$\nu_{N-H}^{Nujol\ Mull}$, cm^{-1}	$\lambda_{max}^{ethanol}$, mμ	ϵ_{max}
I	3370	285	15,350
II	3390	294	16,850
III	3350	322	13,450
IV	3350	291	14,950
V	3360		
VI	3360		
VII	3350	365	15,100
VIII	3330	294	14,300
IX	3360	295	14,500

(1) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98, 1554, 1560 (1957).

(2) W. R. Vaughan and L. R. Peters, *ibid.*, **18**, 393 (1953); W. R. Vaughan and L. R. Peters, *ibid.*, **18**, 405 (1953); W. R. Vaughan and D. I. McCane, *ibid.*, **20**, 143 (1955); W. R. Vaughan, *ibid.*, **20**, 1619 (1955).

(3) C. F. H. Allen, F. W. Spaugler, and E. R. Webster, *ibid.*, **16**, 17 (1951).

mation of a Schiff base between aniline and keto acid followed by cyclization as indicated in eq 2. In our hands, the Schiff base which precipitates on mixing



(2)

these reactants in ethanol proved to cyclize very readily indeed, in agreement with earlier results.[2] For example, solution of the Schiff base of aniline and benzylidenepyruvic acid in ethanol or tetrahydrofuran yields immediately the uv spectrum of the enamine lactone and removal of the solvent yields the enamine lactone as revealed by ir spectroscopy. If the pathway of eq 2 is correct, it follows then that the quantity of Schiff base in equilibrium with reactants must be very small in order to account for the over-all rather slow formation of cyclization product.

Experimental Section

Elemental analyses were performed by Dr. F. Pascher, Bonn, and Dr. A. Bernhardt, Mülheim. Melting points were taken on a hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 237 spectrometer. Uv measurements were made on a Perkin-Elmer 450 uv-visible spectrophotometer. Buffer solutions used for preparative work are those given by M. Clark & Lubs.[4] The Radiometer pH meter 26 was used for measurements of pH. Preparative experiments were performed at water bath temperature (average 80°). The starting materials were purified by distillation or crystallization just before use. The reactants were separately dissolved in suitable volumes of the buffer solutions. All the enamine lactones were purified by crystallization from ethanol–water mixtures.

Kinetic measurements were carried out polarographically with the aid of a Radiometer PO4 polarograph, with DLT1 Drop Life Timer equipped with a cell thermostated at 50°. The drop time was 5 sec, with a mercury reservoir of height 35 cm. Oxygen was removed from the solution by bubbling hydrogen through it for 10 min. The reactions were studied in aqueous solutions which contained benzylidenepyruvic acid, 1.25×10^{-3} M, and aniline or p-aminobenzoic acid in at least 12-fold excess. The values of pH were adjusted with HCl. NaCl was used to maintain a constant ionic strength of 0.5.

The formation of the enamine lactones was followed by observing the disappearance of benzylidenepyruvic acid as a function of time. A sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated in the following manner: the concentration of the remaining acid was plotted on semilogarithmic graph paper against time, the half-time was determined graphically, and the first-order rate constant was obtained from the formula $k = 0.693/t_{1/2}$.

Registry No.—I, 17408-56-9; II, 17408-57-0; III, 17397-52-3; IV, 17397-53-4; V, 17397-54-5; VI, 17397-55-6; VII, 17397-56-7; VIII, 17397-57-8; IX, 17397-58-9.

(4) M. Clark in "International Critical Tables of Numerical Data; Physics, Chemistry, and Technology," Vol. 1, McGraw-Hill Book Co. Inc., New York, N. Y., 1926, p 81.

Substituted Tartranilic Acids. A New Series of Resolving Acids

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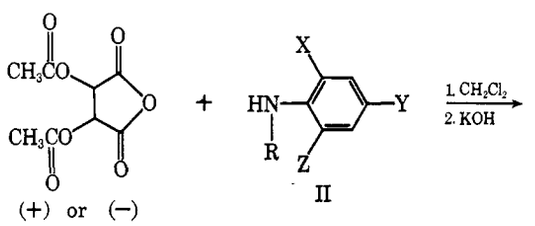
Received May 31, 1968

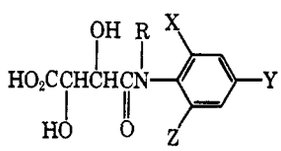
Several substituted tartranilic acids[1] have been synthesized from (+)- and (−)-tartaric acids. We have found these tartranilic acids to be exceptionally useful resolving agents for racemic bases.[2] The substituted tartranilic acids (III) (Tables I and II) were prepared by reaction of a substituted aniline (II) with (+)- or (−)-diacetoxysuccinic anhydride (I) followed by basic hydrolysis of the acetyl groups essentially by the procedure of Pressman, *et al.*[3] The (+)- and (−)-diacetoxysuccinic anhydrides were readily prepared from (+)- and (−)-tartaric acids, respectively.[4]



(+) or (−)

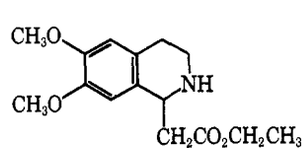
I

II

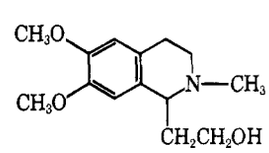


III

Several bases, which had been difficult to separate into their optical isomers, were readily resolved by these acids. Both ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (IV) and 6,7-dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (V) were resolved in good yield by (2*R*:3*R*)-2′-nitrotartranilic acid (no. 1).[5] Battersby, *et al.*,[6] have reported only partial resolution of compound IV after



IV



V

(1) Only a few substituted tartranilic acids have been described in the literature. See K. Landsteiner and J. van der Scheer, *J. Exptl. Med.*, **50**, 407 (1929); L. Casale, *Gazz. Chim. Ital.*, **48**, I, 114 (1918); L. Casale, *ibid.*, **47**, II, 63 (1917); V. B. Fish, J. R. Stevens, and R. G. D. Moore, *J. Amer. Chem. Soc.*, **69**, 1391 (1947).

(2) The resolution of a few alcohols through their esters of (+)-tartranilic acid has been reported. See F. Barrow and R. G. Atkinson, *J. Chem. Soc.*, 638 (1939).

(3) D. Pressman, J. H. Bryden, and L. Pauling, *J. Amer. Chem. Soc.*, **70**, 1352 (1948).

(4) N. Rabjohn, Ed., "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 242. This reference describes the synthesis of (+)-diacetoxysuccinic anhydride from (+)-tartaric acid. The same procedure works equally well with (−)-tartaric acid to give (−)-diacetoxysuccinic anhydride.

(5) (+)-Tartaric acid has the 2*R*:3*R* absolute configuration. All the tartranilic acids prepared from (+)-tartaric acid will therefore have the 2*R*:3*R* configuration. See R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

(6) A. R. Battersby, R. Binks, and T. P. Edwards, *J. Chem. Soc.*, 3474 (1960).