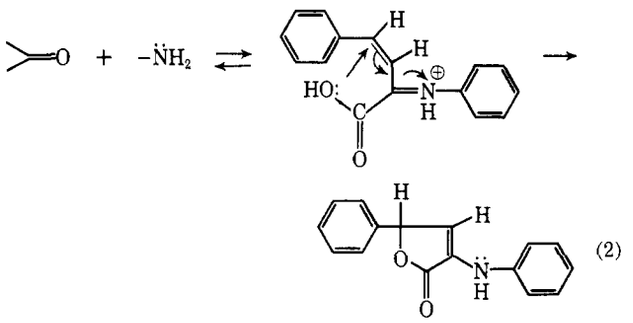
mation of a Schiff base between aniline and keto acid followed by cyclization as indicated in eq 2. In our hands, the Schiff base which precipitates on mixing



(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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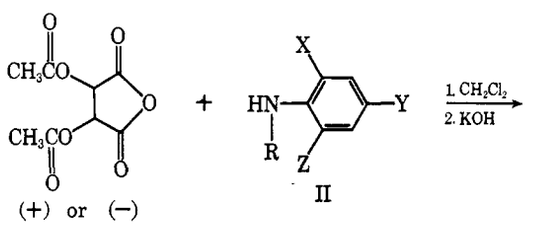
Received May 31, 1968

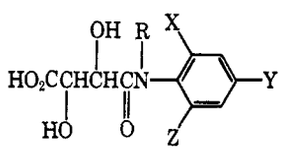
Several substituted tartranilic acids[1] have been synthesized from (+)- and (−)-tartaric acids. We have found these tartranilic acids to be exceptionally useful resolving agents for racemic bases.[2] The substituted tartranilic acids (III) (Tables I and II) were prepared by reaction of a substituted 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 (−)

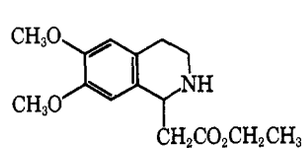
I

II

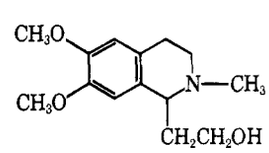


III

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).

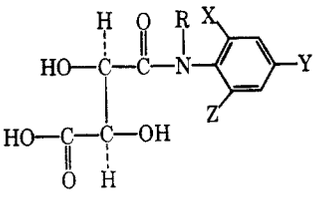
(4) N. Rabjohn, Ed., "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 242. This reference describes the synthesis of (+)-diacetoxysuccinic anhydride from (+)-tartaric acid. The same procedure works equally well with (−)-tartaric acid to give (−)-diacetoxysuccinic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

TABLE I

SUBSTITUTED TARTRANILIC ACIDS DERIVED FROM (+)-TARTARIC ACID[a]

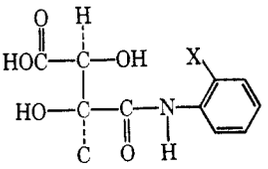


No.	X	Y	Z	R	Yield, %	Mp, °C	Solvent[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$[\alpha]^{25}D$ (c)[c]
1	NO_2	H	H	H	55	196.0–198.0	A[d]	$C_{10}H_{10}N_2O_7$	44.45	3.73	10.37	44.41	3.79	10.31	+90.0° (0.8, water)
2	Cl	H	H	H	87	180.5–182.5	A	$C_{10}H_{10}ClNO_5$	46.26	3.88	5.40	46.22	3.48	5.32	+100.3° (1.6)
3	Br	H	H	H	75	171.5–172.5	A	$C_{10}H_{10}BrNO_5 \cdot H_2O$[e]	37.28	3.76	4.35	37.38	3.97	4.62	+75.6° (1.9)
4	CH_3	H	H	H	40	152.5–154.0	C	$C_{11}H_{13}NO_5$	55.23	5.48	5.86	54.95	5.83	6.00	+108.2° (2.0)
5	H	Cl	H	H	93	193.0–195.0	A–B	$C_{10}H_{10}ClNO_5$	46.26	3.88	5.40	46.62	4.05	5.34	+108.9° (1.6)
6	H	Br	H	H	67	198.5–201.5	A–B	$C_{10}H_{10}BrNO_5 \cdot H_2O$[f]	37.28	3.76	4.35	37.07	3.61	4.32	+90.5° (1.8)
7	Cl	Cl	H	H	79	181–191	A	$C_{10}H_9Cl_2NO_5$	40.84	3.08	4.76	40.84	3.21	4.57	+100.7° (1.6)
8	Cl	Cl	Cl	H	88	176.5–178.5	A	$C_{10}H_8Cl_2NO_5 \cdot H_2O$[g]	34.66	2.91	4.04	34.32	3.01	4.16	+72.4° (2.0)
9	Br	Br	Br	H	25	186.5–189.5	A–B[d]	$C_{10}H_8Br_2NO_5$	26.00	1.75	3.03	26.01	2.04	3.07	+51.1° (1.7)
10	H	H	H	CH_3	11	135.0–137.0	D	$C_{11}H_{13}NO_5$	55.23	5.48	5.86	55.31	5.68	5.87	−97.8° (2.0)

[a] See ref 5. [b] A, water; B, ethanol; C, methyl isobutyl ketone; D, 2-propanol. [c] Unless otherwise indicated, rotations were taken in 95% ethanol. [d] These materials may crystallize containing a small amount of potassium salt. The addition of a few milliliters of hydrochloric acid prevents this. [e] *Anal.* Calcd: H_2O, 5.59. Found: H_2O, 5.66. [f] *Anal.* Calcd: H_2O, 5.59. Found: H_2O, 5.68. [g] *Anal.* Calcd: H_2O, 5.25. Found: H_2O, 5.01.

TABLE II

SUBSTITUTED TARTRANILIC ACIDS DERIVED FROM (−)-TARTARIC ACID[a]



No.	X	Yield, %	Mp, °C	Solvent[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$[\alpha]^{25}D$ (c)[c]
11	Cl	87	179.0–182.5	C	$C_{10}H_{10}ClNO_5$	46.26	3.88	5.40	46.49	3.98	5.35	−100.5° (1.6)
12	Br	67	170.0–171.0	A	$C_{10}H_{10}BrNO_5 \cdot H_2O$[d]	37.28	3.76	4.35	37.45	3.45	4.36	−76.6° (1.9)

[a,b] See footnotes *a* and *b*, Table I. [c] Rotations were taken in 95% ethanol. [d] *Anal.* Calcd: H_2O, 5.59. Found: H_2O, 5.85.

11 recrystallizations of the (−)-dibenzoyltartrate salt. With (2*R*:3*R*)-2′-nitrotartranilic acid we obtained good resolution with only one recrystallization of the salt. Compound V also required only one recrystallization of its (2*R*:3*R*)-2′-nitrotartranilate salt for good resolution.[7]

Experimental Section[8]

Substituted Tartranilic Acids. General Procedure.—A mixture of (+)- or (−)-2,3-diacetoxysuccinic anhydride[4] (21.6 g, 0.1 mol), substituted aniline (0.11 mol), and 200 ml of methylene chloride was heated at reflux for 3–20 hr.[9] The resultant solution was extracted with aqueous potassium hydroxide (0.32 mol of KOH in 200 ml of water) followed by 100 ml of water. The combined aqueous extracts were stirred for 2 hr at 25°, warmed to dissolve any crystalline solid that may have formed, polish filtered, and then acidified with 35 ml of concentrated hydrochloric acid. After cooling the mixture in ice, the crystals[10] were collected, washed with cold water, and recrystallized from the appropriate solvent.

Resolution of (±)-Ethyl 6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (IV).—A warm solution of (±)-ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate[11] (24.8 g, 0.089 mol) in 150 ml of 95% ethanol was treated with a warm solution of (2*R*:3*R*)-2′-nitrotartranilic acid (12.0 g, 0.0445 mol) in 150 ml of 95% ethanol. After cooling the mixture in ice, the crystals were collected (23.9 g) and recrystallized from 300 ml of 75% ethanol (volume per cent) to give pure (2*R*:3*R*)-2′-nitrotartranilic acid salt of the (+)-ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (20.5 g), mp 194.5–196.5°. The first mother liquor was retained for isolation of the (−) isomer.

The above salt was treated with 100 ml of water and 10.5 g of sodium carbonate and extracted with ethyl acetate. The ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated to yield 10 g (81%) of the crystalline (+) isomer, $[\alpha]^{25}D$ +49.1° (*c* 2.3, 95% ethanol). This material was further purified by crystallization of its oxalate salt (95% ethanol) followed by crystallization of the free base from ethyl acetate–*n*-hexane to give 7.5 g (61%) of analytically pure (+)-ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate: mp 85.5–86.5°, $[\alpha]^{25}D$ +50.7° (*c* 1.84, 95% ethanol) [lit.[5] $[\alpha]D$ +23.8° (ethanol)]; oxalate salt, mp 170.5–172.0°, $[\alpha]^{25}D$ +36.2° (*c* 1.53, water).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.70; H, 7.68; N, 4.83.

The mother liquor from the salt formation was concentrated to dryness. The residue was taken up in 100 ml of absolute ethanol, treated with 1 g of (2*R*:3*R*)-2′-nitrotartranilic acid, cooled, filtered, and concentrated to dryness. The residue was

(7) The two resolutions reported here used (2*R*:3*R*)-2′-nitrotartranilic acid as the resolving acid. A few of the other tartranilic acid derivatives have been used with equal success in other resolutions which will be reported elsewhere.

(8) Melting points were obtained on a Fisher–Johns apparatus and are corrected. Optical rotations were measured on a Rudolph polarimeter. The authors wish to thank the microanalytical and spectroscopic departments for their services.

(9) In the case of tribromoaniline chloroform was used as solvent and the reflux time was increased to 96 hr. The reflux times used for the other compounds were as follows: **1** and **8**, 20 hr; **10**, 6 hr; all of the other compounds, 3 hr.

(10) N-Methyltartranilic acid is water soluble and did not crystallize from aqueous solution. In this case the acidified solution was concentrated to a dry powder which was extracted with hot 2-propanol. Cooling of this extract yielded crystalline material which was then recrystallized.

(11) W. J. Gensler and A. L. Blum, *J. Org. Chem.*, **21**, 336 (1956).

taken up in ethyl acetate, washed with dilute sodium carbonate, dried (K_2CO_3), filtered, and concentrated to dryness to leave a crystalline residue (8.5 g), which was recrystallized from ethyl acetate–*n*-hexane to give 5.3 g (43%) of the (−) isomer: mp 84.0–85.5°; $[\alpha]^{25}D$ −49.5° (*c* 2.0, 95% ethanol). This material was purified for analysis through its oxalate salt to give pure (−)-ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (3.5 g): mp 86.0–87.0°; $[\alpha]^{25}D$ −51.0° (*c* 1.88, 95% ethanol) [lit.[6] $[\alpha]D$ −26.9° (ethanol)]; oxalate salt, mp 169.5–171.0°, $[\alpha]^{25}D$ −36.4° (*c* 1.64, water).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.64; H, 7.55; N, 5.14.

Resolution of (±)-6,7-Dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (V).—A warm solution of (±)-6,7-dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline[12] (73.1 g, 0.292 mol) in 375 ml of 95% ethanol was treated with a warm solution of (2*R*:3*R*)-2′-nitrotartranilic acid (39.4 g, 0.146 mol) in 375 ml of 95% ethanol. After cooling the mixture at 5° for 20 hr, the crystals were collected (75.9 g) and recrystallized from 750 ml of 80% ethanol to give the pure (2*R*:3*R*)-2′-nitrotartranilic acid salt of (−)-6,7-dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline[13] (69.8 g, 92%), mp 193.5–195.5°.

The above crystalline salt was decomposed with dilute sodium carbonate and extracted with ethyl acetate. Drying (Na_2SO_4) and concentration of the ethyl acetate extracts gave an oil (30 g) which was converted into its crystalline hydrochloride with concentrated hydrochloric acid (10 ml) in 2-propanol. Recrystallization from absolute ethanol yielded pure (+)-6,7-dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride[13] (25.3 g, 60.5%): mp 177–180°; $[\alpha]^{25}D$ +22.7° (*c* 2.05, chloroform).

Anal. Calcd for $C_{14}H_{21}NO_3 \cdot HCl$: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.67; H, 7.81; N, 4.63.

The mother liquor from the (2*R*:3*R*)-2′-nitrotartranilic acid salt formation was treated with an additional 1.0 g of (2*R*:3*R*)-2′-nitrotartranilic acid and concentrated to dryness. The resultant oil was taken up in ethyl acetate, filtered, washed with dilute sodium carbonate, dried (Na_2SO_4), and concentrated to dryness to leave an oil (33.6 g) which was converted into its hydrochloride in acetone with anhydrous hydrogen chloride. Recrystallization from 95% ethanol yielded pure (−)-6,7-dimethoxy-1-β-hydroxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (24.4 g, 58%): mp 177–179°; $[\alpha]^{25}D$ −22.8 (*c* 2.02, chloroform).

Anal. Calcd for $C_{14}H_{21}NO_3 \cdot HCl$: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.41; H, 7.81; N, 4.67.

Registry No.—III-1, 17447-32-4; III-2, 17447-33-5; III-3, 17477-86-0; III-4, 17447-34-6; III-5, 17447-35-7; III-6, 17447-36-8; III-7, 17447-37-9; III-8, 17447-38-0; III-9, 17447-39-1; III-10, 17447-40-4; III-11, 17447-41-5; III-12, 17447-49-3; (+) IV, 17447-42-6; (+) IV [(2*R*:3*R*)-2′-nitrotartranilic acid salt], 17447-43-7; (+) IV (oxalate), 17447-44-8; (−) IV, 17447-45-9; (−) IV (oxalate), 17447-46-0; (−) V [(2*R*:3*R*)-2′-nitrotartranilic acid salt], 17477-87-1; (+) V hydrochloride, 17447-47-1; (−) V hydrochloride, 17447-48-2.

(12) The synthesis of this material will be described in a later paper.

(13) The rotation of the free base of this isomer is (−) in chloroform. The hydrochloride of this isomer rotates (+) in 95% ethanol.

24ξ-Methyl-9,19-cyclolanostan-3β-yl Palmitate. A New Liquid Crystal

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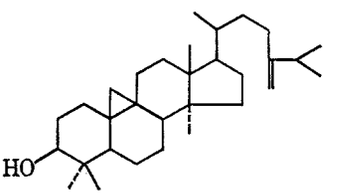
Received April 2, 1968

Since the work of Reinitzer[2] many examples of "liquid crystals" have been described. Friedel concluded that there were three classes of such substances, one of which displayed some rather unique optical properties.[3] Upon melting, these latter substances refracted light while passing from the crystalline to the isotropic liquid state. As an example, cholesteryl laurate was found to turn a violet color when melted.[4] Since a great majority of compounds behaving in this manner were esters of cholesterol, they were referred to as exhibiting a cholesteric phase. This phenomenon has not yet been observed with fatty acid esters of phytosterols. Gray, in collaboration with Kuksis and Beveridge, was unable to detect any cholesteric mesophase with β-sitosteryl laurate or myristate.[5]

During the course of identification of the sterol and triterpene constituents of banana peel we had occasion to examine the large ester fraction isolated from this tissue.[6] The major component of this fraction was purified by alumina column chromatography and crystallization from several solvents. The dihydro derivative was prepared by catalytic reduction. Upon melting this reduced form of the ester, a deep violet color was observed, indicative of a cholesteric phase. This was confirmed by a rather spectacular birefringence pattern in a Nalge–Axelrod apparatus. A cholesteric–isotropic transition temperature of 64° was determined. This effect was more noticeable upon cooling back to the melting point.

The naturally occurring ester was saponified, and a single component was isolated from the nonsaponifiable fraction, subsequently identified as 24-methylene cycloartanol, I (24-methylene-9,10-cyclolanostan-3β-ol).[7]



I

The saponifiable fraction contained only palmitic acid. The synthetic ester was prepared by esterification of I with palmitoyl chloride. The synthetic ester cochromatographed with the naturally occurring ester in several tlc systems. The ir spectra were essentially superimposable. The dihydro form of the synthetic ester also exhibited the violet color upon melting and displayed the same cholesteric–isotropic transition temperature.

The fact that the reduced form of this ester (24ξ-methyl-9,19-cyclolanostan-3β-yl palmitate) displays a color phenomenon associated with a cholesteric phase suggests a stereochemically controlled process. Steric effects have been correlated with nematic behavior.[8] Gray has pointed out that substituents that increase molecular breadth decrease the thermal stability of the paracrystalline state, and thus a mesomorphic effect

(1) NASA Predoctoral Fellow.

(2) F. Reinitzer, *Monatsh. Chem.*, **9**, 421 (1888).

(3) G. Friedel, *Ann. Phys.*, **18**, 273 (1922).

(4) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press Inc., New York, N. Y., 1962, p 45.

(5) A. Kuksis and J. M. R. Beveridge, *J. Org. Chem.*, **25**, 1209 (1960).

(6) *Phytochemistry*, in press.

(7) G. Ohta and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **5**, 40 (1957).

(8) J. S. Dave and M. J. S. Dewar, *J. Chem. Soc.*, 4617 (1954); 4305 (1955).