mixture was refluxed for two hours, then was evaporated to dryness *in vacuo* and the tan-colored solid residue was refluxed with 200 ml. of methanol for two hours. The insoluble sulfanilic acid was separated: weight 5.75 g., neut. equiv. 176 (calcd. 173). Thus, only 2.95 g. of sulfanilic acid entered into reaction. The methanolic solution was concentrated on a steam-bath and enough acetone was added to precipitate the product; yield 3.9 g. (88%, based on reacted sulfanilic acid). The precipitation was repeated thrice to give a white powder of m.p. 197–199° (dec.).

β-(*p*-Chlorophenylimino)-dipropionic Acid.—*p*-Chloroaniline (12.8 g., 0.1 mole), propiolactone (16 g., 0.22 mole) and acetone (50 ml.) were mixed and refluxed for four hours and then kept at room temperature for 24 hours. The solvent was removed and the resulting crystalline solid was treated with about 50 ml. of water at 5°. After several hours, the sticky, light gray solid was collected on a filter and air-dried to give 24.3 g. (yield 90%) of crude product. It was crystallized from aqueous methanol (50 ml. of methanol, 120 ml. of water, and some Norit) to give 19.4 g. of light gray crystalline solid. The sample was recrystallized twice more to yield fine, colorless crystals of m.p. 133–133.5°.

Hydracrylanilide and Aniline.—A mixture of 4.5 g. of hydracrylanilide,[1] m.p. 110–112°, 50 ml. of acetonitrile and 2.55 g. of aniline was refluxed for 25 hours. Then the solvent was removed and sodium carbonate solution was added to the residue. Ether extraction removed 2.3 g. of the original anilide, m.p. and m.m.p. 110–112°. No 3-anilinopropionanilide or 3-anilinopropionic acid was obtained on acidification of the sodium bicarbonate solution to congo red. The solution was clear and nothing in it was extracted by ether.

Reaction with *p*-Toluidine.—Equimolar portions of *p*-toluidine (21.4 g.) and propiolactone (14.4 g.) were dissolved in 100 ml. of ether. The clear solution boiled spontaneously in a few minutes and this boiling lasted an hour. The mixture was kept at 25° overnight, then solvent was removed. The acidic part of the white solid residue was taken up in sodium carbonate solution. There remained 12.5 g. of insoluble amide, and another 1.6 g. was obtained (39.5% total yield) from the aqueous solution by ether extraction. Recrystallization from 300 ml. of water (Norit) gave 12.1 g. of long, colorless needles of m.p. 64–66° (probably a hydrate). After desiccation, the weight dropped to 11.2 g. and the m.p. changed to 101–103°. Three more crystallizations and desiccation brought the m.p. to 104–105°. This was hydracrylo-*p*-toluidide.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.26; N, 7.82. Found: C, 67.3; H, 7.40; N, 8.15.

Benzoyl Derivative.—3-Benzoxypropiono-*p*-toluidide, prepared by benzoylation of the above compound, melted at 135–137° after crystallization from methanol–water.

Anal. Calcd. for $C_{17}H_{17}NO_3$: N, 4.98. Found: N, 5.07.

N-*p*-Tolyl-β-alanine.—The sodium carbonate solution was made acid to litmus and the oil which appeared was taken up in ether, from which there was obtained 21.4 g. (59.5%) of brown sirup. No satisfactory way was found to crystallize this acid, but its salt was prepared by treating 10 g. of it in 60 ml. of absolute alcohol with sodium ethoxide from 1.2 g. of sodium. The sodium salt was quite soluble but 2.0 g. of white solid separated.

Anal. Calcd. for $C_{10}H_{12}NNaO_2$: Na, 11.44. Found: Na, 11.39.

These yields of 39.5% toluidide and 59.5% acid are in contrast to the yield of 14.5% of toluidide obtained when acetone was taken as solvent rather than ether.

Acknowledgments.—One of us (S. H.) received a research fellowship from funds supplied by Swift and Company. The propiolactone was kindly supplied by B. F. Goodrich Company and was used as received without distillation. Microanalyses were performed by Miss J. Sorensen and Mrs. C. White.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, REED COLLEGE]

Attempts to Resolve Racemic Amines by Means of Optically Active, Acidic Synthetic Polymers[1a]

BY J. F. BUNNETT[1b] AND JEAN LOVENDAHL MARKS

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Optically active phenol–formaldehyde type resins were prepared from both optical isomers of β-(*p*-hydroxyphenyl)-butyric acid (I) and from N-*p*-toluenesulfonyl-L-tyrosine (II). No substantial amount of racemization occurred during polymerization or subsequent treatments which the resins received. The optically active resins were placed in columns and solutions of racemic α-pipecoline, α-methylbenzylamine and other amines passed through slowly in the hope that one optical isomer might be preferentially bound to the resin. The first samples of amine which broke through were, however, devoid of optical activity. A theoretical discussion of the experiments is offered.

One would expect that if a racemic substance in solution were brought into contact with an optically active adsorbent, one constituent of the racemate would be more strongly adsorbed[2] than its antipode. This would constitute a method of resolution. The literature records a number of efforts,[3] some failures, others partially successful, to achieve such resolution using naturally occurring adsorbent materials such as wool, *d*-quartz and cellulose. The present work is a study, the first of its kind,[4] of the possibility of using synthetic optically active polymers as agents for the resolution of racemic substances.

In planning these experiments, a column type of operation was chosen so that any resolving effect would be magnified, as in the case of the usual ion exchange resins. It was clear that the synthetic optically active polymers should have the insolubility and chemical stability customary in ion exchange materials, and that the polymers should not be racemized by the reagents to which they would be exposed. For a monomer from which a polymer would be prepared, there were again three require-

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[1] (a) Presented before the Division of Organic Chemistry at the 121st Meeting of the American Chemical Society, Milwaukee, Wis., April, 1952. (b) Chemistry Department, University of North Carolina, Chapel Hill, N. C.

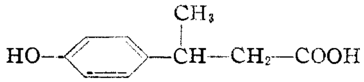
[2] For present purposes, the term "adsorption" embraces strong binding forces such as salt formation as well as van der Waals and other weak binding forces.

[3] G. M. Henderson and H. G. Rule, *J. Chem. Soc.*, 1568 (1939); W. Bradley and G. C. Easty, *ibid.*, 499 (1951); M. Kotake, T. Sakan, N. Nakamura and S. Senoh, THIS JOURNAL, **73**, 2973 (1951); R. Tsuchida, M. Kobayashi and A. Nakamura, *J. Chem. Soc. Japan*, **56**, 1339 (1935), from *C. A.*, **30**, 926 (1936); G. Karagunis and G. D. Coumoulos, *Nature*, **142**, 162 (1938); V. Prelog and P. Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).

[4] A. K. Macbeth, J. A. Mills and R. Pettit, *J. Chem. Soc.*, 3538 (1950), suggested the desirability of such a study while the present work was in progress.

ments: asymmetry, a function allowing it to engage in polymerization,[5] and a functional group to bind molecules of the racemic substance.

Polymers were prepared from two optically active monomers, β-(*p*-hydroxyphenyl)-butyric acid (I) and N-*p*-toluenesulfonyl-L-tyrosine (II). The former was prepared by demethylation of the known β-(*p*-methoxyphenyl)-butyric acid, and was resolved by crystallization of its brucine salts. Having its asymmetry beta to its carboxyl, I was very resistant to racemization as demonstrated by the fact that a solution of dextro I in 10% sodium hydroxide did not suffer any change in rotation during 5.67 hours at 100°. II was prepared from L-tyrosine by known reactions. Although, because its asymmetry is alpha to a carboxyl group, II is more readily racemized than I, experiments showed that it did not suffer much racemization under conditions to which it was exposed in these experiments.



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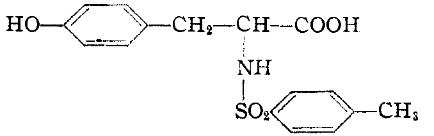

II

From both isomers of I, phenol–formaldehyde type polymers were prepared, with one-half mole of phenol per mole of I added to the polymerization recipe as a cross-linking agent. The first stage of polymerization was acid-catalyzed, and the second stage base-catalyzed, using hexamethylenetetramine. A soluble linear polymer formed from a similar recipe from which phenol had been omitted had a high specific rotation, showing that the polymerization conditions did not destroy the optical activity of the monomer.

From II, a phenol–formaldehyde type polymer was also prepared,[6] using phenol as a cross-linking agent and acid catalysis for both stages of polymerization. Retention of a large degree of optical activity during polymerization was shown by the high specific rotation of the small amount of soluble polymer formed as a by-product, and by an experiment in which II suffered only 17% racemization when it was submitted to the usual polymerization conditions except that formaldehyde was omitted.

Attempted Resolution of Racemic Amines.—Because the salt forms of the resins from both I and II occupied more space than the carboxyl forms, it was not possible to use the resins in straight columns. In both cases when a basic solution was allowed to pass through a straight column loosely packed with a resin in its carboxyl form, the swelling was so great that flow stopped. It was therefore necessary to place the resins in special columns which consisted of vertically arranged series of shallow resin beds. In these, swelling of the resins resulted in vertical expansion with little influence on flow rate.

In resolution experiments, solutions of racemic amines were passed slowly through the columns. The portion of effluent containing the first substantial amount of amine was carefully examined to see whether the amine possessed optical activity, for the first amine to break through would be expected to show the greatest optical activity if resolution occurred. Mere polarimetric examination of this portion of effluent was not sufficient because the specific rotations of the amines in the solvents used were either very low or unknown.[7] Instead, it was necessary to convert the amine to a solid derivative whose specific rotation in a convenient solvent was known, or to examine the amine as a concentrated solution in a solvent in which its specific rotation was known to be high.

Resolutions of α-pipecoline, α-methylbenzylamine and 4-dimethylamino-2,2-diphenylvaleronitrile were attempted by means of the polymer from II. In no case did the appropriate solution of the amine or its derivative show a rotation greater than experimental error. The design of the experiments was such that about 3% resolution could have been detected.

Similarly, resolutions of α-pipecoline and α-methylbenzylamine were attempted by means of the resin derived from dextro I. Again no rotation greater than experimental error was observed under conditions which would have revealed 3% of resolution.[8]

Discussion

The experiments offer no evidence that any resolution occurred whatsoever. Although this result was at first surprising, it seemed after reflection to be not unreasonable. Let us consider the interaction of a *dl*-amine (*dl*-RNH_2) with a *d*-polymer acid (*d*-Pol-COOH). Upon the first contact of the amine with the polymer acid, the salts *d*-RNH_3^+ *d*-Pol-COO^- and *l*-RNH_3^+ *d*-Pol-COO^- would be formed. As more amine came into contact with these salts, certain equilibrium reactions would occur, of which only the following would result in chemical change

$$l\text{-RNH}_3^+\ d\text{-Pol-COO}^- + d\text{-RNH}_2 \rightleftharpoons d\text{-RNH}_3^+\ d\text{-Pol-COO}^- + l\text{-RNH}_2 \quad (1)$$

The forward reaction represents displacement of a levo amine molecule from the polymer salt by a dextro amine molecule, and *vice versa*. Since *d*-Pol-COO^- occurs on both sides of this equation, it can be eliminated, giving

$$\text{l-RNH}_3^+ + d\text{-RNH}_2 \rightleftharpoons d\text{-RNH}_3^+ + l\text{-RNH}_2 \quad (2)$$

By inspection, the equilibrium constant for equation (2) is unity. Since the concentrations of the entities on the left are in the beginning equal to the concentrations of the corresponding entities on the right, and since the activity coefficients of the uncharged amine molecules are probably equal, any displacement of the equilibrium from its midposition would have to arise from a difference in

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[5] The optically active monomer need not possess the three or more positions for chain growth that are necessary for cross-linking and therefore insolubility; the three-dimensional structure can be achieved by the incorporation of special cross-linking agents in the polymerization recipe.

[6] This appears to be the first instance of the preparation of a phenol–formaldehyde type polymer from an acyl derivative of tyrosine. A. E. Brown, This Journal, **68**, 1011 (1946), prepared from tyrosine itself and formaldehyde in alkaline solution polymers with various degrees of solubility. Drastic treatment of tyrosine with formaldehyde and concentrated hydrochloric acid results in the formation of a second ring, a tetrahydroisoquinolinecarboxylic acid being produced; *cf.* A. Pictet and T. Spengler, *Ber.*, **44**, 2030 (1911).

[7] Calculation showed, for instance, that a typical portion of effluent, examined in a 1-dm. tube, would have shown a rotation of only 0.13° if there had been complete resolution.

[8] By means of resins derived from I, resolutions of *s*-butylamine, α-*p*-tolylethylamine and 2-aminoheptane were also attempted. In these cases, however, only the aqueous or aqueous alcoholic effluent from the column was examined polarimetrically, and the polarimeter used could be read only to 0.05°. No optical activity was observed, but for reasons stated above the most that could be concluded from these experiments is that no large degree of resolution occurred.

the thermodynamic activities of the ionic species in equation (2). For example, if $a_{l-\mathrm{RNH}_3^+} > a_{d-\mathrm{RNH}_3^+}$, a shift in the equilibrium so as to increase the concentrations of the species on the right side would have to occur in order to maintain the equilibrium constant.

It is profitable to enquire in what situation these activities might differ, considering that the ammonium ions exist in the presence of *d*-Pol-COO$^-$ ions. If the steric fit of *d*-RNH$_3^+$ with *d*-Pol-COO$^-$ were better than the fit of *l*-RNH$_3^+$ with *d*-Pol-COO$^-$, the activity of *l*-RNH$_3^+$ would be greater because this ion would be less closely associated with the available negative ions. A difference in steric fit would be expected if the sites of asymmetry in both ammonium cations and polymer anions were close to the charge-carrying functional groups, and if some of the groups attached to the asymmetric carbon atoms were large so that they would project forward of the functional groups. In such a case, because of the specific interaction of these forward-projecting groups, one ammonium ion would be able to make a closer approach to the carboxylate anion of the polymer than could its antipode. However, in the present experiments the groups about the asymmetric carbon atoms were too small to cause much interference forward of the functional groups.[9] From these considerations the failure to observe resolution may be understood.

The situation described above differs from two known methods of resolution to which it might seem to be closely related. The first is the resolution of amines by crystallization of their salts with an optically active acid. In this case, whether an asymmetric ammonium ion is allowed to enter a crystal with an asymmetric anion depends on the total fit of the two ions. Not only is the fit forwards of their functional groups important; the fit at the back and sides also matters. Thus it is not necessary that the site of asymmetry be near the acidic or basic functional group in order for resolution to be achieved by this common technique. The second is the resolution of rather large molecules by fractional adsorption on optically active solids by relatively weak chemical forces. In this method, it is probably necessary to have several points of contact per molecule in order to achieve the necessary binding energy, and it is therefore probable that the closeness of fit with the asymmetric surface is more sensitive to the sense of asymmetry of the molecules in solution than in the present experiments in which there was only one point of attachment per molecule.[10]

Experimental[11]

β-(*p*-Hydroxyphenyl)-butyric Acid (I).—A Reformatsky reaction[12,13] between *p*-methoxyacetophenone (270 g.), ethyl bromoacetate (300.6 g.) and zinc (129.5 g.) produced ethyl *p*-methoxy-β-methylcinnamate (254 g., 64%). Saponification and sodium amalgam reduction[13] produced β-(*p*-methoxyphenyl)-butyric acid (153 g., 69%). For demethylation, 145 g. of the latter was combined with 620 cc. of 48% hydrobromic acid and 1600 cc. of glacial acetic acid. After five hours refluxing, 3 l. of water was added and the volume was reduced to about two liters by distillation under reduced pressure. The brown crystals which separated on cooling were collected on the suction filter and the filtrate was extracted with ether. Water was added to the residue from evaporation of the ether extracts, causing the formation of a tan solid. Further concentration of the original reaction liquor yielded additional brown solid. These several crops of product were combined and recrystallized three times from water, using charcoal each time. White crystals of β-(*p*-hydroxyphenyl)-butyric acid (I), m.p. 136–136.5°, weighing 98.3 g. (72.6%) were obtained.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65: H, 6.71. Found[14]: C, 66.63, 66.78; H, 7.00, 6.88.

Resolution of I.—Seventy-two grams (0.4 mole) of I was dissolved, with heating, in 1400 cc. of water and 157.9 g. (0.4 mole) of brucine was added. The solution was maintained close to its boiling point and stirred for three hours. The suspended solid gradually disappeared and its place was taken by an oil in suspension. The hot solution was then decanted from the viscous oil; on cooling, it deposited a nearly white crystalline material. The viscous oil was dissolved in 300 cc. of warm ethanol and somewhat more than an equal volume of water was added; a tan precipitate gradually formed. Both the tan and white precipitates were recrystallized repeatedly (seven to nine times) from water or dilute ethanol, most often from 25% ethanol (by volume), with occasional charcoal treatments to remove colored impurities. There resulted 74.5 g. of white crystalline material, m.p. about 100–112°, having $[\alpha]^{20}\mathrm{D}$ −35° (*c* 2.67, ethanol), a constant value which the latter recrystallizations did not change. Analysis indicated that it was a hydrate containing 2.5 molecules of water.

Anal. Calcd. for $C_{33}H_{38}O_7N_2 \cdot 2^1/_2H_2O$: C, 63.95; H, 6.99. Found[14]: C, 64.01; H, 6.80.

This brucine salt was heated with a solution of 15 cc. of sulfuric acid in 500 cc. of water until solution was complete. After cooling, the solution was extracted with three 100-cc. portions of ether. The residue from evaporation of the ether extracts was recrystallized twice from water, furnishing 19.8 g. of white crystalline levorotatory I, m.p. 150–150.5°, $[\alpha]^{25}\mathrm{D}$ −34.4° (*c* 4.12, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found[14]: C, 66.80; H, 6.62.

The liquors from recrystallization of the above brucine salt were repeatedly concentrated, and each time cooling caused a small additional portion of crystalline material to separate. Further concentration, however, caused the separation of oils which slowly solidified to an amorphous solid, the crude brucine salt of the dextrorotatory acid. This crude salt was decomposed by means of dilute sulfuric acid, yielding dextrorotatory I which, after two recrystallizations from water, had m.p. 150–151°, $[\alpha]^{25}\mathrm{D}$ +33.1° (*c* 3.37, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found[14]: C, 66.64; H, 6.66.

Equal quantities of the dextro and levo forms of I were combined and recrystallized; the resulting material had m.p. 135–135.5°.

Polymers from I.—A mixture of 9.01 g. (0.05 mole) of levo I, 2.35 g. (0.025 mole) of phenol, 12.2 g. of formalin (0.15 mole of formaldehyde) and 5 drops of 6 *M* sulfuric acid was refluxed one hour. The resulting white polymer was, after it had been allowed to cool and become brittle, ground and intimately combined with 1.63 g. of hexamethylenetetramine. The dry mixture was heated in two large test-tubes 30 minutes at 190–195°. After the resulting orange-brown resin had been soaked in 5% hydrochloric acid for 30 minutes, it was extracted with acetone in a Soxhlet extractor until the extract was no longer colored. It was then boiled three times with portions of 150 cc. of 10% sodium hydroxide. Finally it was soaked with 150 cc. of 6 *M* hydrochloric acid to regenerate the carboxyl form of the resin from its sodium salt.

In similar fashion, a polymer was prepared starting with 11.5 g. of dextro I. After the resolution experiments, this

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[9] This conclusion is supported by examination by models.

[10] There is recent evidence that, in certain types of enzyme action, "three-point contact" between substrate and enzyme is necessary. *Cf.* P. E. Wilcox, C. Heidelberger and V. R. Potter, THIS JOURNAL, **72**, 5019 (1950); A. G. Ogston, *Nature*, **162**, 963 (1948).

[11] Melting points are uncorrected.

[12] S. Lindenbaum, *Ber.*, **50**, 1270 (1917).

[13] E. H. Woodruff and E. Pierson, THIS JOURNAL, **60**, 1075 (1938); J. M. van der Zanden, *Rec. trav. chim.*, **60**, 505 (1941).

[14] Analysis by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y.

polymer (wt. 13.1 g.) was removed from the column and titrated with sodium hydroxide by the Mattson technique.[15] An equivalent weight of 236 ± 4 was found; the calculated equivalent weight for 0.5 phenol unit per unit of I in the polymer (the same ratio as in the polymerization recipe) is 248; for 0.4 phenol unit per unit of I it is 237.

That little or no racemization occurred during the preparation of these polymers was shown in the following manner: A sample of levo I of m.p. 149–150°, $[\alpha]^{20}\text{D}$ −30°, was condensed with formaldehyde according to the same procedure used for the main polymer preparations except that phenol was excluded from the recipe. There resulted the usual Novolac stage polymer; it was soluble in alcohol and had $[\alpha]^{20}\text{D}$ −28°. Further treatment with hexamethylenetetramine at 195° gave a yellow-brown polymer which was also soluble in alcohol. Its rotation was difficult to determine with accuracy because of the color of its solution; however, an approximate $[\alpha]^{20}\text{D}$ −30° was observed.

N-*p*-Toluenesulfonyl-L-tyrosine (II).—L-Tyrosine, $[\alpha]^{24}\text{D}$ −10.5°,[16] was converted to the methyl ester hydrochloride, 53.5 g. of which was converted to the methyl ester of the sulfonamide II by the method which Fischer and Lipschitz[17] used for the corresponding ethyl ester. A small amount of the methyl ester of II crystallized at room temperature from the chloroform solution in which it was formed, but most of it was obtained as an amorphous cake by evaporation of the chloroform. The cake was dissolved in a solution of 32 g. of potassium hydroxide in 300 cc. of water and the resulting solution heated in a boiling water-bath for 28 minutes. After filtration to remove insoluble impurities, acidification precipitated II. After recrystallization from water and from 30% ethanol, 34.3 g. of II, m.p. 182–183.5°, $[\alpha]^{27}\text{D}$ −8.9° (*c* 6.63, 0.5 *M* sodium hydroxide) was obtained. This optical purity is greater than reported by Fischer and Lipschitz,[17] but less than that of the best sample we obtained (see below).

Methyl Ester of II.—The small amount which crystallized in the preceding preparation was recrystallized from chloroform, from which crystallization is slow, and then from a mixture of equal volumes of chloroform and carbon tetrachloride. White crystals resulted; m.p. 131.5–132.5°, $[\alpha]^{23}\text{D}$ +4.1° (*c* 9.98, methanol).

Anal. Calcd. for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48. Found[18]: C, 58.55; H, 5.46.

Saponification of the methyl ester with a slight excess of 1 *M* potassium hydroxide on the steam-bath for 15 minutes produced II of $[\alpha]^{24}\text{D}$ −11.0° (*c* 6.26, 0.5 *M* sodium hydroxide). This was the highest rotation we observed for II; other samples were obtained from saponifications of greater duration, during which some racemization probably occurred. Saponification was incomplete in 10 minutes on the steam-bath.

A Polymer from II.—A mixture of 33.79 g. (0.101 mole) of II of $[\alpha]^{27}\text{D}$ −8.9°, 5.63 g. (0.0598 mole) of phenol, 28.4 g. of formalin (0.256 mole of formaldehyde), 43.1 g. of glacial acetic acid and 3 cc. of 6 *N* sulfuric acid was refluxed for 34 minutes by means of an oil-bath at 125–138°. During this time a sticky white polymer slowly separated. The reflux condenser was removed and heating was continued another 42 minutes with the bath at 132–140°, causing most of the solvent to boil off and the polymer to become tough. When cold, the hard polymer was removed from the flask with a chisel, and soaked successively in 0.5 *M* ammonium hydroxide, in dilute hydrochloric acid, and in acetone. The acetone discharged a greenish discoloration, converting all the polymer to an orange-brown color. The resin was then collected on a suction filter, air-dried, ground in a mortar, and sifted. The golden powder (11.1 g.) which passed the 80-mesh sieve was rejected, while the 32.2 g. of yellow and golden brown granules which passed 40 mesh but not 80 mesh was retained. This 40–80 mesh material was suspended in very dilute ammonium hydroxide and allowed to settle; the fine particles which did not settle rapidly were decanted off and this process was repeated until most of the "fines" were removed. The resin was then ready to put in a column.

Upon evaporation of the acetone extract, a small amount of amorphous tan solid was deposited. Of a 0.618-g. sample of this, all but 0.082 g. dissolved in 25 cc. of 0.5 *M* sodium hydroxide, and the resulting solution had a rotation of +0.46° in a 1 dm. tube; thus $[\alpha]\text{D}$ +21°.

Effect of Polymerization Conditions on II.—A mixture of 1.66 g. of II of $[\alpha]^{31}\text{D}$ −8.5°, 0.23 g. of phenol, 2.1 g. of glacial acetic acid, 0.9 g. of water and 3 drops of 6 *N* sulfuric acid was refluxed two hours in an oil-bath at 132–137°. From this mixture, II was recovered and recrystallized from 30% ethanol; m.p. 183–184°; $[\alpha]^{30}\text{D}$ −7.0°. Thus the specific rotation decreased by 17%.

Effect of Amines on the Optical Purity of II.—A mixture of 0.63 g. of II (sample of low optical purity) and 0.51 g. of piperidine with water to 10 cc. formed a dark yellow solution with $\alpha^{21}\text{D}$ +0.25 ± 0.03° (1-dm. tube); after 37 days at room temperature, this solution had $\alpha^{23}\text{D}$ +0.23 ± 0.05°. A mixture of 0.61 g. of II (sample of low optical purity) and 0.73 g. of α-methylbenzylamine with ethanol to 10 cc. formed a light yellow solution with $\alpha^{20}\text{D}$ +0.48 ± 0.01° (1-dm. tube); after 36 days at room temperature, this solution had $\alpha^{24}\text{D}$ +0.52 ± 0.03°.

The Polymer Columns.—Because the polymers swelled on reaction with bases,[19] it was necessary to construct special columns consisting of a number of short units arranged one above another. Each unit was made by constricting a six-inch test-tube (approx. 18 mm. diameter) about four inches from the open end, making a break at the constriction, and sealing on a short length of 8-mm. glass tubing. By means of a rubber stopper connection, the 8-mm. tube of each unit led into the wide mouth of the unit below. The bottom unit of the column had a buret-type stopcock in place of the usual short length of 8-mm. tubing. Above the top unit, there was a reservoir of about 200-cc. capacity. In each unit, a small piece of clay plate and a wad of glass wool supported the granular polymer.

The sample of polymer from II was distributed amongst ten units in one column to an average depth of 4 cm. (carboxyl form), and that from dextrorotatory I amongst eleven units in another column, the depth in each unit being about 2 cm.

In preparing a column for a resolution experiment, we passed 0.5 *M* hydrochloric acid through in order to remove bases, and then rinsed with distilled water until the effluent tested negative for chloride ion.

Attempts to Resolve Amines by Means of the Polymers from I.—A solution of 17.1 g. of α-methylbenzylamine in 300 cc. of 20% ethanol was allowed to pass slowly through the column packed with resin from dextro I. Because of difficulties in controlling flow rate by means of a stopcock, the rate of flow was sometimes very low but never exceeded 0.5 cc. per minute in this or any other resolution experiment. Flow was stopped at night. When the original solution of amine had entirely drained from the reservoir, it was followed by 20% ethanol. Titration showed that the first 260 cc. of effluent contained a negligible amount of the amine. The next 35 cc. contained 0.035 g. of amine, and then two 25-cc. portions of effluent contained, respectively, 0.050 and 0.155 g. These three portions were combined, with the solutions resulting from titration of aliquots of each, and shaken vigorously with 2 cc. of 20% sodium hydroxide and 0.50 g. of benzoyl chloride. A granular, cream-colored solid separated; when air-dried, it weighed 0.49 g. and smelled somewhat of ethyl benzoate; m.p. 105.5–113°. A solution of 0.288 g. of this in benzene to 10 cc. showed, in a 1-dm. tube, a rotation of +0.01 ± 0.02°. From data of Pope and Read,[20] by interpolation, a rotation of 1.18° would have been observed had the solid been an optically pure antipode of N-(α-methylbenzyl)-benzamide.

Similarly, a solution of 14.0 g. of α-pipecoline in 290 cc. of water was passed through the column, being followed by water when the amine solution had all drained from the reservoir. The first 264 cc. of effluent contained negligible amounts of the amine; two 25-cc. portions of effluent collected immediately thereafter contained, respectively, 0.052 and 0.431 g. of amine. These two portions, with the

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(15) Described by R. Kunin and R. J. Myers, "Ion Exchange Resins," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 150–153.

(16) Reported for L-tyrosine by W. H. Stein, S. Moore and M. Bergmann, This Journal, **64**, 724 (1942): $[\alpha]^{24}\text{D}$ −10.8 ± 0.2°, for a 5% solution in 4% hydrochloric acid.

(17) E. Fischer and W. Lipschitz, *Ber.*, **48**, 360 (1915).

(18) Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

(19) The salt forms of resins derived from I occupied about twice the volume of the carboxyl forms, and the resin from II swelled about 20% on exposure to dilute ammonia.

(20) W. J. Pope and J. Read, *J. Chem. Soc.*, **103**, 451 (1913).

solutions resulting from titration of aliquots of each, were combined, treated with an excess of concentrated hydrochloric acid, and evaporated to dryness under reduced pressure. After 1.5 cc. of 50% potassium hydroxide solution had been added, the contents of the flask were distilled at atmospheric pressure. Addition of 1 g. of potassium hydroxide pellets to the distillate caused it to separate into two layers. The mixture was extracted with four portions of commercial *n*-hexane, the combined hexane extracts were dried over potassium hydroxide, and they were then diluted with *n*-hexane to 10 cc. in a volumetric flask. The resulting solution contained 0.432 g. of α-pipecoline, and showed, in a 1-dm. tube, a rotation of +0.02 ± 0.02°. Leithe[21] reported for (+)-α-pipecoline, $[\alpha]^{15}\text{D}$ +35.7°; accordingly, if there had been 100% resolution, this solution would have displayed a rotation of 1.54°.

Attempts to Resolve Amines by Means of the Polymer from II.—A solution of 17.1 g. of α-methylbenzylamine in 300 cc. of 20% ethanol was allowed to pass slowly through the column. Portions constituting the first 338 cc. of effluent tested acid to litmus. The next three portions, 82 cc. in all, tested basic and were separately treated with sodium hydroxide and benzoyl chloride under Schotten–Baumann conditions, but oils were produced which solidified only on long standing. However, the following 28-cc. portion, treated the same way, gave an immediate nearly white precipitate which, when air-dried, weighed 0.246 g.; m.p. 112.5–118°. A solution of this amide in benzene to a total volume of 10 cc. showed, in a 1-dm. tube, a rotation of −0.05 ± 0.02°; however, after this solution had been washed with sodium hydroxide solution, and again (because of evaporation losses) made up to 10 cc. with benzene, its rotation was 0.00 ± 0.02°. Although a slight loss of N-(α-methylbenzyl)-benzamide occurred during sodium hydroxide washing, the loss of optical activity is believed to be due to removal by washing of a trace of soluble polymer which had contaminated the crude amide. From the data of Pope and Read,[20] by interpolation, the benzene solution before washing would have shown a rotation of 1.06° had the solid been an optically pure antipode of the amide; after sodium hydroxide washing its rotation would have been somewhat less.

In a similar experiment, the benzoyl derivative of the first α-methylbenzylamine to break through was recrystallized prior to polarimetric examination, a procedure which admittedly might have eliminated a small excess of one optical antipode. The resulting amide, in benzene solution of concentration such that the rotation would have been 0.48° had there been complete resolution, displayed a rotation of 0.00 ± 0.00°.

A solution of 14 g. of α-pipecoline in 290 cc. of water was allowed to pass slowly through the column of resin from II. After 345 cc. of effluent had been collected, a 15-cc. portion containing 0.35 g. of amine was treated much as in the above experiment concerning the resin from I, in order to prepare a solution in hexane. Ten cubic centimeters of the hexane solution contained 0.269 g. of amine, and in a 1-dm. tube showed a rotation of 0.00 ± 0.01°; according to the data of Leithe,[21] the solution would have shown a rotation of 0.96° if there had been complete resolution.

A solution of 39.3 g. of 4-dimethylamino-2,2-diphenylvaleronitrile in 600 cc. of 95% ethanol was allowed to pass through the column which had been thoroughly washed with ethanol. The amino nitrile did not appear to be retained on the resin, for after only 107 cc. of effluent had been collected, a 25-cc. portion containing 0.50 g. of nitrile was obtained. In a 1-dm. tube, this solution showed a rotation of +0.03 ± 0.03°, whereas had the nitrile been completely resolved, the rotation would have been, from data of Pohland, Marshall and Carney,[22] 1.00°; further, the nitrile recovered from this solution and recrystallized from dilute alcohol, showed (*c* 2.92, ethanol), in a 1-dm. tube, a rotation of −0.01 ± 0.02°, whereas the rotation would have been 1.46° had there been complete resolution.

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[21] W. Leithe, *Monatsh.*, **50**, 40 (1928).

[22] A. Pohland, F. J. Marshall and T. P. Carney, THIS JOURNAL, **71**, 460 (1949).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Mechanism of the Decarboxylation of α,β- and β,γ-Unsaturated Malonic Acid Derivatives and the Course of Decarboxylative Condensation Reactions in Pyridine[1]

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The decarboxylation of several half-esters of α,β-unsaturated malonic acids in pyridine has been investigated for the purpose of determining the influence of the α,β-ethylenic linkage on such systems. The decarboxylation of ethyl hydrogen isopropylidenemalonate (II) proceeds rapidly in pyridine (111°) and affords a mixture of ethyl β-methyl-β-butenoate (IV) and ethyl β,β-dimethylacrylate (III) (ratio, 3:1). The reaction has been studied kinetically and has been found to take place by way of the β,γ-unsaturated acid, which decarboxylates as the conjugate base. The mesomeric anion produced by decarboxylation accepts a proton *irreversibly* at C_α or C_γ to give IV or III. Ethyl hydrogen isopropenylmethylmalonate (VIII) upon decarboxylation also yields a mixture of the isomeric β,γ- and α,β-unsaturated esters (ratio, 1:1). The rates of decarboxylation of II, ethyl hydrogen isopropylmalonate and VIII have been found to differ by factors of ten and to increase in the order: ethyl hydrogen isopropylmalonate, II, VIII. The decarboxylations of ethyl hydrogen mesitylidenemalonate (VI) and ethyl hydrogen 2,6-dichlorobenzylidenemalonate (VII) which can lose carbon dioxide only by a direct mechanism are extremely slow in pyridine near the boiling point. The significance of the results of the present study on the mechanism of decarboxylative condensation reactions is pointed out. Two new routes to α,β-unsaturated malonic acid derivatives have been devised and are illustrated herein.

The mechanism and ease of decarboxylation of α,β-unsaturated malonic acid derivatives are of special concern from both a preparative and theoretical viewpoint. The presence of an α,β-ethylenic linkage in the malonic acid system introduces interesting structural variations on the relatively well studied case of the saturated malonic acids[2] which are almost certain to manifest themselves in a divergence of mechanism. Furthermore, knowledge of the course of decarboxylative condensation reactions, such as that due to Doebner, Knoevenagel and Verley,[3] which are of fundamental significance in synthetic work, would be advanced considerably by an understanding of the behavior of α,β-unsaturated malonic acid derivatives in various

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[2] B. R. Brown, *Quart. Rev.*, **5**, 131 (1951).

[3] Reviewed by J. R. Johnson in R. Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 226–228.