Acetylation.—A solution of 0.5 g. of the pyrazole derivative in 30 ml. of acetic anhydride was refluxed for two hours. The excess of acetic anhydride was removed under reduced pressure, and the cooled oily residue was treated with crushed ice and kept aside for a half-hour. The solid (*ca.* 0.39 g.), was filtered off, washed thoroughly with cold water and crystallized from alcohol in colorless crystals, m.p. 109°. The acetyl derivative is insoluble in aqueous sodium hydroxide solution (10%) and gave no color with ferric chloride. It gave an orange color with sulfuric acid.

Anal. Calcd. for $C_{29}H_{28}N_2O_4S$: C, 69.60; H, 5.60; N, 5.60; S, 6.40. Found: C, 70.02; H, 5.58; N, 5.60; S, 6.43.

Action of Hydroxylamine Hydrochloride on (a) 7,8-Benzothioncoumarin.—A solution of 1 g. of the thioncoumarin in 40 ml. of ethyl alcohol was treated with a solution of 0.3 g. of hydroxylamine hydrochloride, and 0.5 g. of sodium carbonate in 5 ml. of water. The reaction mixture was refluxed (steam-bath) for four hours, during which time yellow crystals separated out. The reaction mixture was cooled, filtered off and the reaction product was crystallized from ethyl alcohol as pale-yellow needles (*ca.* 0.95 g.), m.p. 222° (brown melt), and analyzed correctly for the expected oxime.[38]

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.93; H, 4.26; N, 6.63. Found: C, 74.10; H, 4.38; N, 6.65.

(b) IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*).—A mixture of 0.5 g. of the sulfide, 0.1 g. of hydroxylamine hydrochloride 30 ml. of ethyl alcohol and five drops of freshly distilled pyridine was refluxed for three hours (steam-bath). The cooled reaction mixture was poured into ice-cold water, and acidified with dilute acetic acid; the deposit formed was filtered (*ca.* 0.41 g.), and crystallized from ethyl alcohol in colorless crystals, m.p. 162°. The isoxazole derivative (XIIIa or XIIIb) was soluble in hot benzene; its alcoholic solution gave no color with sulfuric acid.

Anal. Calcd. for $C_{25}H_{23}NO_3S$: C, 71.94; H, 5.51; N, 3.35; S, 7.67. Found: C, 71.82; H, 5.36; N, 3.24; S, 7.51.

Acetylation.—The acetyl derivative of the isoxazole derivative (XIIIa or XIIIb) was similarly obtained as previously described in the case of (XIa or XIb). It was obtained in colorless crystals from ethyl alcohol; m.p. 119°. It was insoluble in aqueous sodium hydroxide solution (10%) and gave an orange color with sulfuric acid.

Anal. Calcd. for $C_{27}H_{25}NO_4S$: C, 70.59; H, 5.45; N, 3.05; S, 6.97. Found: C, 70.53; H, 5.43; N, 3.02; S, 6.76.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF STANFORD UNIVERSITY]

Synthesis of the Racemic *p*-Dimethylaminobenzylidene-N,N′-bis-(1-phenylethyl)-malonamides

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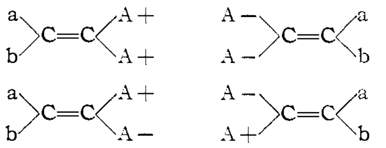
Examples of the racemic forms of compounds having the structure abC=CA₂, where a and b are different non-dissymmetric groups and A is a dissymmetric group, have been prepared. Attempts to resolve one of the racemic forms were unsuccessful because of the instability of its salts.

It has been pointed out[2] that whereas a ketone having the structure $A_2C{=}O$, where A is a dissymmetric group, should exist in a racemic and a *meso* modification, the oxime of the *meso*-ketone as well as that of the racemic ketone should be resolvable, because the *syn* and *anti* forms of the *meso*-ketone are non-superposable mirror images. Apparently examples of *syn* and *anti* or of *cis* and *trans* isomerism arising from two enantiomorphic groups have not been reported in the literature.

The present work reports the preparation of the racemic forms I and II of a compound of the type $abC{=}CA_2$.



I

II

The compound chosen for study was the *p*-dimethylaminobenzylidene derivative of N,N′-bis-(1-phenylethyl)-malonamide. The malonamide of (1-phenylethyl)-amine should exist in a racemic and a *meso* modification. Reaction of racemic (1-phenylethyl)-amine with ethyl malonate gave two forms, one melting at 163–165° and the other at 139.5–140.° In order to determine which form was *meso* and which racemic, the active amides were prepared from the active amines. They melted at 135–136° and when mixed in equal amounts, they gave the racemic amide melting at 164–165°. Hence the amide melting at 139.5–140° is the *meso* form.

Condensation of the amides with *p*-dimethylaminobenzaldehyde gave two benzylidene derivatives, both of which are racemic. Since the benzylidene derivative from the racemic amide was the more easily prepared, initial attempts at resolution were made on this form. However, no stable salts could be obtained with (+)-tartaric, (−)-malic, (−)-mandelic, or (+)-camphor-10-sulfonic acid. A colorless hydrochloride was obtained when dry hydrogen chloride was passed into a benzene solution of the amine, but when the hydrochloride was added to water the yellow amine precipitated. Apparently, the two amide groups acting through the conjugated system reduce the basicity of the *p*-dimethylamino group to the point where salt formation does not take place in hydroxylic solvents.

Accordingly the amine was converted to the methiodide, and the quaternary iodide converted to the (+)-camphor-10-sulfonate. Attempts to separate the salt into its diastereoisomers were not promising. Because of these difficulties no attempt was made to resolve the racemic form of the benzylidene derivative from the *meso*-amide. It is hoped to prepare the carboxylic analog of these compounds, because the factors that reduce the basicity of the dimethylamino group should increase the acidity of the carboxyl group and permit easier resolution.

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[2] R. L. Shriner and R. Adams, p. 240 in Gilman's Organic Chemistry, 2nd Ed., 1943, John Wiley and Sons, New York, N. Y.

Experimental

Dextro, Levo and Racemic N,N'-Bis-(1-phenylethyl)-malonamides.—A mixture of 7.54 g. (0.047 mole) of ethyl malonate and 5 g. (0.041 mole) of (+)-(1-phenylethyl)-amine, $[\alpha]^{25}\mathrm{D}$ +39.95°, was heated in an oil-bath at 130° for 24 hours. A light yellow, viscous solution resulted, which was dissolved in a minimum volume of hot petroleum solvent (b.p. 77–110°) and allowed to crystallize. The product was recrystallized five times to give 0.74 g. (10%) of the **dextro amide**, m.p. 135–136°, $[\alpha]^{25}\mathrm{D}$ 146.4° (*c* 4.65 in abs. ethanol).

Anal.[3] Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.35; H, 7.26; N, 8.88.

The **levo amide**, obtained from ethyl malonate and (−)-(1-phenylethyl)-amine, $[\alpha]^{25}\mathrm{D}$ −37.6°, by the same procedure, melted at 135–136°, $[\alpha]^{25}\mathrm{D}$ −146.5° (*c* 1.07 in abs. ethanol).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.39; H, 7.26; N, 9.14.

When a mixture of equal amounts of the dextro and levo amides was dissolved in a minimum volume of hot petroleum solvent (77–110°), and allowed to crystallize, the racemic amide was obtained, m.p. 164–165°.

Racemic and *meso*-N,N'-Bis-(1-phenylethyl)-malonamide.—A mixture of 120 g. (0.75 mole) of ethyl malonate and 182 g. (1.5 moles) of racemic (1-phenylethyl)-amine in a 500-cc. flask was heated in an oil-bath at 120–140° for 24 hours. After cooling, the cream-colored mass was broken up and dissolved in a minimum volume of boiling acetone. The filtered solution after standing overnight deposited a crop of crystals which was recrystallized from acetone. The yield of fine white needles melting at 151–162° was 64.5 g. (27.8%).

Concentration of the filtrates gave a dark brown solid mass which was dissolved in a minimum volume of boiling ethyl acetate, and the solution was allowed to stand for 24 hours. The crop of crystals was removed and recrystallized from ethyl acetate to give 37.8 g. (16.3%) of fine white crystals, m.p. 132–137°.

The higher-melting fraction was subjected to triangular crystallization from acetone. The first six of nine fractions melted in the range 163–166°. They were combined and crystallized eight times from acetone without appreciably changing the melting point. The final product melted at 163–165°. A mixture with an equal amount of the racemic amide prepared from the active amines melted at 164–165°.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.44; H, 7.04.

Recrystallization of the lower-melting fraction from ethyl acetate gave a mixture of small white balls and needles. They were removed by filtration and dried. When placed in a flask and agitated with a small amount of warm carbon tetrachloride, the needles dissolved. The mixture was filtered rapidly, and the filtrate was allowed to crystallize at 0°. The carbon tetrachloride extraction procedure was repeated twice, and the product finally was crystallized five times from carbon tetrachloride to give the pure **meso amide** melting at 139.5–140°.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.59; H, 7.29.

(±)-*p*-Dimethylaminobenzylidene-N,N'-bis-(1-phenylethyl)-malonamide from Racemic N,N'-Bis-(1-phenylethyl)-malonamide.—A mixture of 1.49 g. (0.01 mole) of *p*-dimethylaminobenzaldehyde, 3.1 g. (0.01 mole) of racemic N,N'-bis-(1-phenylethyl)-malonamide (m.p. 164–165°), 1 cc. of piperidine, 0.5 cc. of acetic acid and 50 cc. of benzene in a 125-cc. flask was heated in an oil-bath at 130–135° for three hours. As the benzene evaporated, more was added from time to time to assist in the removal of water. On cooling, a dark brown solid was obtained which was dissolved in a minimum volume of boiling 95% ethanol and allowed to crystallize. Five recrystallizations gave 0.84 g. (19%) of fine yellow rhombohedrons, m.p. 191.6–192.1°.

Anal. Calcd. for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.46; H, 7.19; N, 9.32.

The same product was obtained in 29% yield from the crude 151–162° fraction of N,N'-bis-(1-phenylethyl)-malonamide made from (±)-(1-phenylethyl)-amine.

When ethyl *p*-dimethylaminobenzylidenemalonate[4] was heated with (±)-(1-phenylethyl)-amine, the product isolated was ***p*-dimethylaminobenzylidene-(±)-(1-phenylethyl)-amine**, m.p. 78–78.5° after crystallization from 2-propanol.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.99, 80.83; H, 7.72, 7.86; N, 11.00.

No stable salts of the benzylidene derivative of the racemic amide could be obtained with (+)-tartaric acid, (−)-malic acid, (−)-mandelic acid or (+)-camphor-10-sulfonic acid. A colorless hydrochloride was prepared by passing dry hydrogen chloride into a benzene solution of the amine. When the hydrochloride was dissolved in water, the yellow amine precipitated.

The **methiodide** was prepared by dissolving 6.8 g. of the benzylidene derivative in 200 cc. of warm methanol, adding 2.8 g. of methyl iodide and heating in sealed tubes at 60° for 40 hours. The combined reaction mixture was concentrated to one-third its volume and allowed to crystallize. The product was crystallized four times from methanol to give 3.95 g. (36%) of pale yellow platelets, m.p. 198–204° dec.

Anal. Calcd. for $C_{29}H_{34}IN_3O_2$: C, 59.69; H, 5.88; N, 7.20; I, 21.75. Found: C, 59.60, 59.62; H, 6.04, 6.06; N, 7.09, 7.19; I, 21.69.

The methiodide was converted to the (+)-camphor-10-sulfonate by mixing separate hot solutions of 0.75 g. (0.0013 mole) of the methiodide and 0.45 g. (0.0014 mole) of silver (+)-camphorsulfonate in methanol. The silver iodide was removed by filtration, and the filtrate evaporated to dryness. Crystallization of the pale yellow glass from carbon tetrachloride gave 0.56 g. (88%) of crystals, m.p. 203–218° dec., which were found by analysis to be impure. Attempts to obtain pure diastereoisomers by crystallization from 95% ethanol and from ethyl acetate were unsuccessful.

Anal. Calcd. for $C_{39}H_{49}N_3O_6S$: C, 68.09; H, 7.18. Found: C, 69.40; H, 6.87.

(±)-*p*-Dimethylaminobenzylidene-N,N'-bis-(1-phenylethyl)-malonamide from *meso*-N,N'-Bis-(1-phenylethyl)-malonamide.—This product was prepared by a procedure analogous to that used to prepare the benzylidene derivative from the racemic amide, except that benzene was not used to remove the water. The reaction was incomplete and the first crop of crystals from ethanol was unreacted amide. Concentration of the mother liquor gave a product which, after two crystallizations from methanol, melted at 184.4–185°. A mixture with the product from the racemic amide, m.p. 188–190°, melted at 167–180°.

Anal. Calcd. for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.66; H. 7.29; N, 9.50.

STANFORD, CALIF.

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[3] Microanalyses by Microchemical Specialties, Berkeley 3, Calif.

[4] E. J. Wayne and J. B. Cohen, *J. Chem. Soc.*, **127**, 459 (1925).