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

Restricted Rotation in Aryl Olefins. X. β-Methyl-β-arylacrylic Acids[1]

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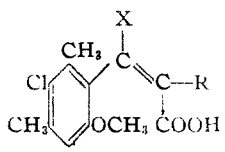
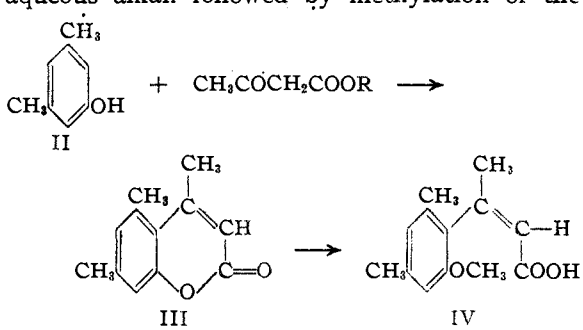
Several compounds of Type I have been described in previous papers.[1,3] Those in which X = Cl, R = CH_3; X = Cl, R = H; X = Br,



I

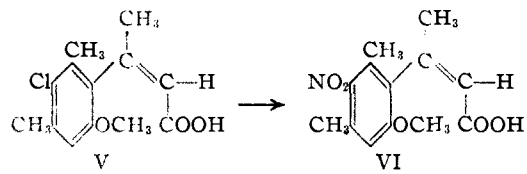
R = H were resolved and gave relatively unstable optical isomers; those in which X = OCH_3, R = CH_3; X = OCH_3, R = H; X = SCH_3, R = H could not be resolved. This research had as its objective the synthesis of compounds of Type I in which X = CH_3 and R = H or CH_3. The synthetic methods previously employed are not applicable to the formation of these compounds. An adaptation of the von Pechmann reaction as illustrated with 3,5-dimethylphenol in II–IV was selected as a suitable procedure.[4] The coumarin (III) was hydrolyzed with aqueous alkali followed by methylation of the



II III IV

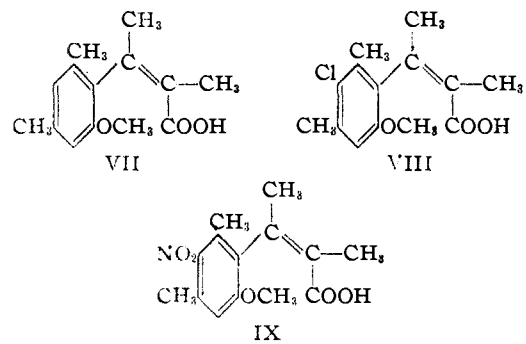
hydroxyl group with dimethyl sulfate. The corresponding β-methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (V) could not be synthesized in a similar manner using 4-chloro-3,5-dimethylphenol since a chromone always resulted from the initial condensation.[4] The coumarin (III), however, could be nitrated in the 6-position and by reduction, diazotization and replacement by chlorine, the 6-chlorocoumarin was obtained. Both the nitrated and chlorinated coumarins were hydrolyzed and methylated to give V and VI.

By substitution of ethyl methylacetoacetate for ethyl acetoacetate, condensation with 3,5-dimethylphenol gave a coumarin which after hydrolysis and methylation yielded the α,β-di-



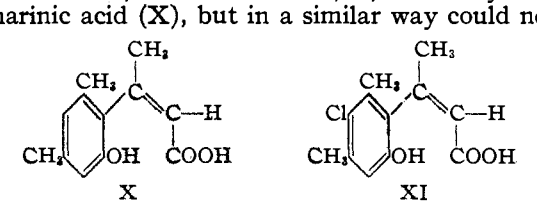
V VI

methylacrylic acid (VII). The coumarin intermediate could be nitrated and the nitro group replaced by chlorine; hydrolysis and methylation of these derivatives gave VIII and IX.



VII VIII IX

In all of the arylacrylic acids described in previous papers the geometrical configuration about the double bond has been assumed to have the carboxyl group *cis* to the aryl group. This orientation was assigned mainly on the basis of the optical stability of the molecules and a study of models.[5] The evidence for the carboxyl group being *cis* to the aryl group in compounds IV–IX is much more sound. The opening of a coumarin should lead to this configuration. Jordan and Thorpe,[6] by hydrolysis of III followed by careful acidification, isolated the β-2,4-trimethylcoumarinic acid (X), but in a similar way could not



X XI

obtain the corresponding coumarinic acid from the 6-nitrocoumarin. These experiments were repeated and confirmed. The 3-chloro-β-2,4-trimethylcoumarinic acid (XI) was prepared but the corresponding α,β-2,4-tetramethylcoumarinic acid always reverted to the coumarin on acidification of the alkaline solution. The coumarinic acid (X) formed the coumarin instantaneously in warm glacial acetic acid to which a drop of hydrochloric acid was added. Cyclization also took place on

(1) For previous paper in this series see Adams and Ludington, THIS JOURNAL, 67, 794 (1945).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(3) Adams and Gross, THIS JOURNAL, 64, 1786 (1942).

(4) Adams and Mecorney, *ibid.*, 66, 802 (1944).

(5) Adams, *et al.*, *ibid.*, 62, 53 (1940); 63, 1589, 2773 (1941); 64, 1791, 1795 (1942); 65, 2208, 2383 (1943).

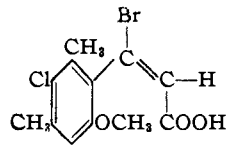
(6) Jordan and Thorpe, *J. Chem. Soc.*, 107, 387 (1915).

boiling for one hour in ethanol or standing overnight at room temperature in the same solvent. This acid (X) when methylated under the same conditions used in the hydrolysis and methylation of the coumarin (III) gave the same methyl ether (IV). It would appear from these results that no change in configuration had occurred during the preparation of compounds IV–IX. The arylacrylic acids IV–IX are also converted to the corresponding coumarins in 60–80% yield by refluxing for fifteen to twenty-five minutes with 48% hydrobromic acid.

Attemps to resolve compounds IV–IX were attended with great difficulty. By the standard procedure, using a variety of alkaloids and solvents, viscous liquids resulted in many cases. Where crystalline salts were isolated they showed a great tendency to dissociate with the precipitation of the alkaloid. The resolution of α,β-dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (VII) was successful when the crude brucine salt was extracted with large volumes of anhydrous ether followed by spontaneous evaporation of the solvent. Decomposition gave a *levo* acid $[\alpha]^{28}D$ −51°, whose half-life was seventy-four minutes in *n*-butanol at 44°. The molecule thus is less stable than the α-methyl-β-chloro-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (formula I, where X = Cl, R = CH_3) which under similar conditions has a half-life of one hundred and seventy-three minutes.[3] Although these molecules are not directly comparable, since the latter has a chlorine in the 3-position in the ring whereas the former does not, it has been demonstrated previously by a comparison of the optical stabilities of β-chloro-β-(2,3,4,6-tetramethylphenyl)-acrylic acid and β-chloro-β-(3-bromo-2,4,6-trimethylphenyl)-acrylic acid, which have essentially the same half-lives, that groups in the ring have only small effects. Since the relative rates of racemization of VII and I (X = Cl, R = CH_3) are at least qualitatively correct it may be deduced that the β-methyl group has less influence than the β-chlorine on restriction of rotation. The β-bromine has been demonstrated to be larger than the β-chlorine[1] and therefore the influence on restricted rotation of β-substituents in this arylacrylic acid series may be listed as bromine > chlorine > methyl in contrast to bromine > methyl > chlorine for these groups in the *ortho* positions in the biphenyl series.[7]

The half-life of VII in *n*-butanol at 22° was found to be seven hundred minutes. The half-life of β-bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (Ia) under essentially the same conditions had a value of four hundred and twenty minutes. Assuming that the effect of the chlorine in the ring of the latter compound has a negligible influence, then the greater stability of VII, in spite of the fact that it contains

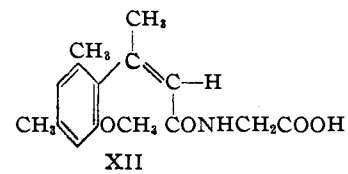
(7) Stoughton and Adams, THIS JOURNAL, 54, 4426 (1932); Yuan and Adams, *ibid.*, 54, 4434 (1932).



Ia

a β-methyl group in place of the larger β-bromine in Ia, serves to illustrate again the marked stabilizing influence of the α-methyl group.

The β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (IV) did not give crystalline salts with alkaloids. It was converted to the corresponding glycine (XII) which formed a crystalline brucine salt. The salt showed no signs of mutarotation and on acidification the acid separated gradually as an oil which did not crystallize. Similarly α,β-dimethyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid (IX) gave no crystalline salts. The brucine salts of β-methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid (VI) and β-methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (V) were obtained crystalline but were difficult to purify. They showed no mutarotation and no optically active acids resulted when decomposed with cold hydrochloric acid.



XII

Owing to the great instability of β-chloro-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid which has a half-life of only nine minutes in *n*-butanol at 20°, it is probable that compounds IV, V and VI are incapable of resolution.

Experimental

β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic Acid (IV).—A mixture of 10 g. of 4,5,7-trimethylcoumarin,[4] 64 cc. of water and 6 g. of sodium hydroxide was refluxed with stirring until the coumarin dissolved. In the course of one hour 26 cc. of dimethyl sulfate was added dropwise to the refluxing solution. When the solution became acidic, as evidenced by the formation of an oil, it was kept alkaline by addition of portions of 20% aqueous sodium hydroxide put in over a period of two hours. At the end of this time 50 cc. more of alkali was introduced and the stirring and refluxing continued for one hour. The acrylic acid was thus subjected to the action of alkali for a total of five hours. Upon addition of the solution to crushed ice containing concentrated sulfuric acid, a white solid was obtained. It was redissolved in alkali, filtered, reprecipitated with acid, and crystallized from aqueous ethanol; colorless cubic crystals, m. p. 201.5° (cor.). The yield of product was 9 g. (77%).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.68; H, 7.46.

β-Methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid (V).—A mixture of 1 g. of 6-chloro-4,5,7-trimethylcoumarin,[4] 10 cc. of water and 1 g. of sodium hydroxide was refluxed with stirring for one and one-half hours until all solid material dissolved. During the course of one hour, 3 cc. of dimethyl sulfate was added and then gradually 10 cc. of 20% aqueous sodium hydroxide to keep the solution alkaline. The heating and stirring were continued for two hours longer and the solution which had

turned orange was added to crushed ice containing acetic acid. The solid was collected, treated with 5% aqueous sodium bicarbonate solution and filtered. The filtrate was acidified and the solid collected and crystallized from aqueous ethanol. To obtain colorless material the product was crystallized repeatedly from petroleum ether (b. p. 60–110°), m. p. 164–165° (cor.); yield 0.7 g. (65%).

Anal. Calcd. for $C_{13}H_{15}ClO_3$: C, 61.29; H, 5.94; Cl, 13.92. Found: C, 61.53; H, 5.99; Cl, 14.09.

β-Methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic Acid (VI).—From 10 g. of 6-nitro-4,5,7-trimethylcoumarin,[4] 6 g. of sodium hydroxide and 100 cc. of water (the solution was a deep cherry-red in alkali) 26 cc. of dimethyl sulfate, and 100 cc. of 20% aqueous sodium hydroxide was obtained 8 g. (71%) of the nitroarylacrylic acid; yellow needles from ethanol, m. p. 202–203° (cor.). It was found advisable to work up the ethanolic mother liquors.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.70. Found: C, 59.03; H, 5.75.

3,4,5,7-Tetramethylcoumarin.—To 95 g. of 3,5-dimethylphenol and 110 g. of freshly-distilled ethyl methylacetoacetate was added 450 cc. of concentrated sulfuric acid with cooling and stirring. The solution was allowed to stand several days at room temperature and then was added to cracked ice and filtered. The solid was washed thoroughly with dilute aqueous sodium hydroxide, then water and crystallized from acetone or ethanol. It was found necessary to recrystallize the material several times to remove traces of the trimethylcoumarin. After five crystallizations, the yield was 14.5 g. (11%) of short, thick, white crystals; m. p. 157° (cor.). Clayton[8] reports m. p. 154°. The low yield may have been due to the presence of ethyl acetoacetate in the ethyl methylacetoacetate.

α,β-Dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic Acid (VII).—From 2 g. of 3,4,5,7-trimethylcoumarin, 13 cc. of water, 1.2 g. of sodium hydroxide and 5 cc. of dimethyl sulfate, was obtained 1.5 g. (71%) of the α,β-dimethylarylacrylic acid as white cubic crystals from ethanol; m. p. 194–196° (cor.).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 71.77; H, 7.74. Found: C, 71.74; H, 7.79.

6-Nitro-3,4,5,7-tetramethylcoumarin.—Nitration of the tetramethylcoumarin was attended with unexpected difficulties. It appears that the nitro group enters the molecule in more than one position. To 13 g. of 3,4,5,7-tetramethylcoumarin dissolved in 100 cc. of concentrated sulfuric acid cooled by means of a salt–ice-bath from −10 to −5° was added with stirring in the course of six hours 20 cc. of a nitrating mixture comprised of three parts by volume of sulfuric acid to one part of nitric acid (sp. gr. 1.42). After one additional hour the solution was allowed to warm to room temperature in the course of forty-five minutes and added to crushed ice. After several crystallizations from acetone, the long colorless needles melted at 154.5° (cor.). The yield was 4 g. (27%).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.18; H, 5.26; N, 5.71.

α,β-Dimethyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic Acid (IX).—From 2.0 g. of 6-nitro-3,4,5,7-tetramethylcoumarin, 1.2 g. of sodium hydroxide, 15 cc. of water, 5 cc. of dimethyl sulfate and 20 cc. of aqueous sodium hydroxide, was obtained 2 g. (89%) of arylacrylic acid; yellow prisms from ethanol, m. p. 190–191° (cor.).

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.01. Found: C, 60.41; H, 6.28; N, 5.04.

6-Amino-3,4,5,7-tetramethylcoumarin.—To 1 g. of 6-nitro-3,4,5,7-tetramethylcoumarin was added 1 g. of tin, 1 g. of stannous chloride, 10 cc. of concentrated hydrochloric acid and 3 cc. of ethanol. After standing overnight the mixture was shaken mechanically for six hours at room temperature when all the tin had dissolved. The crude amine hydrochloride was removed by filtration and dissolved in hot water. Tarry matter was removed with aid of Norite followed by filtration. The solution was cooled and rendered basic by portion-wise addition, with stirring, of solid sodium bicarbonate. The yellow solids thus obtained contained inorganic material. The free amine was readily extracted with boiling ethanol and upon standing overnight the extract deposited 0.5 g. (55%) of fine pale-yellow needles, m. p. 154–155° (cor.).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.97; H, 7.22; N, 6.45.

6-Chloro-3,4,5,7-tetramethylcoumarin.—To 50 cc. of water and 10 cc. of concentrated hydrochloric acid heated to boiling was added 1.5 g. of 6-amino-3,4,5,7-tetramethylcoumarin. The clear solution was then cooled rapidly to 0° with vigorous stirring and the amine hydrochloride separated in a finely-divided state. In the course of one hour, 0.5 g. of reagent quality sodium nitrite dissolved in 10 cc. of water was added until the diazotized solution gave an immediate starch iodide test. The cold diazonium solution was then introduced with vigorous stirring into 2 g. of freshly prepared cuprous chloride dissolved in 10 cc. of concentrated hydrochloric acid. Immediate evolution of nitrogen took place and a white solid separated. The pale-yellow needles purified from ethanol melted at 135–136° (cor.); yield, 1 g. (60%).

Anal. Calcd. for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54; Cl 14.98. Found: C, 65.86; H, 5.67; Cl, 15.18.

Ozonization of 6-Chloro-3,4,5,7-tetramethylcoumarin.—A solution of 0.1 g. of 6-chloro-3,4,5,7-tetramethylcoumarin in 50 cc. of ethyl acetate was subjected to a stream of ozone 2.5% by volume at the rate of 100 cc. per minute for three hours. The ozonide was decomposed with 20 cc. of methanol–water (1:1) and the solvent removed on the steam-bath with an air blast. The intermediate pyruvate was not isolated. A solution of the resulting oil in 0.5 g. of sodium hydroxide and 10 cc. of methanol–water (1:1) was refluxed for one hour. Upon evaporation of the solvent and acidification, a solid was obtained that was extracted overnight with petroleum ether (b. p. 30–60°). On concentration of the solvent, 50 mg. of yellowish needles m. p. 110–112° (cor.) were obtained. Although this material melted slightly higher than 5-chloro-4,6-dimethyl-2-hydroxyacetophenone (m. p. 106–110°); the melting point of a mixture was not depressed; m. p. 111–112° (cor.).

α,β-Dimethyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid (VIII).—This substance was prepared by the action of alkali and dimethyl sulfate on 6-chloro-3,4,5,7-tetramethylcoumarin. From 0.1 g. of the coumarin was obtained 50 mg. of colorless cubic crystals. Purified from ethanol it melted at 160–160.5° (cor.).

Anal. Calcd. for $C_{14}H_{17}ClO_3$: C, 62.56; H, 6.37; Cl, 13.19. Found: C, 62.55; H, 6.50; Cl, 13.04.

β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-N-acrylylglycine (XII).—A mixture of 2 g. of β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (IV) and 5 cc. of colorless thionyl chloride was warmed on the steam-bath for ten minutes. It was then added slowly with cooling to a solution of 10 g. of glycine in 5 g. of sodium hydroxide and 20 cc. of water. An oily substance separated and the stirring was continued until the solution remained clear. Following filtration and acidification a gum separated that solidified by rubbing with dilute ethanol. The solid was powdered and was extracted for fifteen hours with petroleum ether (b. p. 30–60°) in a Soxhlet continuous extraction vessel. The remaining solid was twice crystallized from toluene. It formed small crystals, m. p. 141–142° (cor.); yield 1 g. (40%). By concentration of the extract, 0.1 g. of starting material was recovered.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.75; H, 6.91; N, 5.05. Found: C, 65.03; H, 6.62; N, 5.13.

β-2,4-Trimethylcoumarinic Acid (X).—A mixture of 3 g. of 4,5,7-trimethylcoumarin, 3 g. of sodium hydroxide and 60 cc. of water was warmed on the steam-bath overnight and filtered into a beaker containing concentrated hydrochloric acid. Upon shaking, a solid crystallized readily which was completely soluble in 5% aqueous sodium bicarbonate. Upon acidification of the bicarbonate

(8) Clayton, *J. Chem. Soc.*, **93**, 2016 (1908).

solution and crystallization from dilute aqueous ethanol, 2 g. (65%) of white flakes was obtained, m. p. 138° (cor.) with evolution of gas. The crystallization was carried out as follows; the coumarinic acid was dissolved in warm ethanol, water was added and the solution shaken with cooling. Care must be taken not to boil the ethanolic solution since ring closure is effected in this way. Jordan and Thorpe[6] report m. p. 128° with evolution of water vapor.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.23; H, 7.12.

The coumarinic acid (X) reverts to the coumarin instantaneously by warming in glacial acetic acid to which a drop of hydrochloric acid has been added. Water is added and white needles of 4,5,7-trimethylcoumarin separate directly. The coumarin closure also can be effected by boiling in absolute ethanol for one hour or standing overnight at room temperature in the same solvent.

Methylation of the phenolic group with dimethyl sulfate and alkali as in the direct conversion of the coumarin results in formation of β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (IV).

3-Chloro-β-2,4-trimethylcoumarinic Acid (XI).—A mixture of 1 g. of 6-chloro-4,5,7-trimethylcoumarin, 1 g. of sodium hydroxide and 20 cc. of water was warmed on the steam-bath for four hours. The solution was filtered into hydrochloric acid and the product crystallized on standing several hours. The solid was collected, dissolved in 5% aqueous sodium bicarbonate and reprecipitated with acid. Crystallization in the manner described for trimethylcoumarinic acid gave a quantitative yield of product, m. p. 149.5–150° (cor.).

Anal. Calcd. for $C_{12}H_{13}O_3Cl$: C, 59.88; H, 5.44. Found: C, 60.05; H, 5.64.

Coumarins from the Arylacrylic Acids.—The arylacrylic acids IV, V, VI, and VII could be converted back to the corresponding coumarins under the following conditions. About 0.5 g. of the arylacrylic acid was refluxed from fifteen to twenty-five minutes with 15 cc. of 48% hydrobromic acid when solution was effected. Upon cooling, needles of the coumarin crystallized from the reaction mixture. The yields could be increased by the addition of water. The solids were collected and washed thoroughly with 5% aqueous sodium bicarbonate.. The coumarins were crystallized from ethanol; yields, 60–80%.

Resolution of α,β-Dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic Acid (VII).—The usual procedure for forming salts with quinine, quinidine, cinchonine, cinchonidine, brucine, strychnine, *d*-α-phenylethylamine and *l*-menthylamine in ethyl acetate, ethanol, methanol, chloroform, isoamyl alcohol and acetone failed to give crystalline products.

A mixture of 2.495 g. of α,β-dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (VII) and a solution of 4.19 g. of anhydrous brucine in 50 cc. of absolute ethanol was warmed on the steam-bath. The solvent was removed under vacuum over calcium chloride at room temperature. Absolute ether was added to the oily semi-solid and upon triturating the solution, crystalline material resulted. The ether treatment was repeated several times and the solids finally dried over calcium chloride at which point no oily material was present. The white solid was ground to a fine powder in a mortar and extracted with 300 cc. of absolute ether. A residue of 1 g. remained that proved to be brucine. The ether-soluble portion was concentrated to 200 cc. and seeded. Upon standing overnight in the icebox, clusters of crystals were deposited that also proved to be brucine. The solution was filtered and concentrated to 20 cc. and immediate crystallization took place; 0.5 g. of Fraction A, m. p. 139–141° (cor.). Concentration and seeding yielded 0.28 g. of a second crop of crystals, Fraction B, m. p. 134–138°. The salt fractions were washed with absolute ether and analyzed as such. Although the salts were quite soluble in warm ether, recrystallization produced brucine, the salt evidently decomposing.

Anal. Fraction A. Calcd. for $C_{14}H_{18}O_3 \cdot C_{23}H_{26}N_2O_4$: C, 70.68 H, 7.05. Found: C, 70.38; H, 6.95.

Mutarotation.—A solution of 0.1 g. of Fraction A made up to 10 cc. in absolute ethanol gave α_D −0.45; *l*, 1; $[\alpha]^{23}D$ −45°. After one hour and forty minutes, α_D −0.43; after five hours and forty minutes, α_D −0.38; after six hours and forty minutes, α_D −0.36; after seventeen hours and forty minutes, α_D −0.31; after twenty-three hours, α_D −0.28; after twenty-six hours, α_D −0.27; after forty-one hours, α_D −0.23; after forty-seven hours and thirty minutes, α_D −0.23; after fifty hours and fifty minutes, α_D −0.23. Similar results were obtained in repeating the experiment, with the equilibrium reached in forty hours.

***l*-α,β-Dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic Acid (VII).**—Fraction A was decomposed by shaking with ice and concentrated hydrochloric acid and then filtered. The process was repeated until the filtrate gave a negative test for brucine; the active acid melted at 194–195° (cor.). This was probably not optically pure material.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.83; H, 8.03.

Rotation. 0.10 g. made up to 10.5 cc. with *n*-butanol at 22° gave α_D −0.49; *l*, 1; $[\alpha]^{22}D$ −51°.

Racemization of *l*-α,β-Dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic Acid (VII).—A solution of 0.15 g. of the *l*-acid made up to 5 cc. with *n*-butanol gave the following values at 44°. The α_D values are averages of five or more individual readings: initially α_D −0.75°; after thirty minutes, α_D −0.558; after forty-five minutes, α_D −0.488; after sixty minutes, α_D −0.418; after seventy-five minutes, α_D −0.372; after ninety minutes, α_D −0.318; after one hundred and five minutes, α_D −0.276; after one hundred and sixty minutes, α_D −0.192; after two hundred and twenty-five minutes, α_D −0.110; after two hundred and ninety minutes, α_D −0.058; after one thousand three hundred and twenty minutes, α_D 0.0. The average half-life calculated from these figures, assuming a reversible first order reaction, was seventy-three minutes. Repetition gave identical results.

The racemization was also carried out at 22°. A solution of 0.10 g. made up to 10.5 cc. of *n*-butanol gave α_D −0.49; after four hours and twenty minutes, α_D −0.38; after five hours and fifty minutes, α_D −0.34; after six hours and thirty minutes, α_D −0.32; after eight hours, α_D −0.28. The average half-life calculated from these figures was seven hundred minutes.

β-Methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic Acid (VI); Brucine Salt.—A solution of 5 g. of β-methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid (VI) and 7.43 g. of anhydrous brucine in absolute ethanol was refluxed on a steam-bath and the solvent then removed in a vacuum desiccator over calcium chloride at room temperature. After several days a hard, crystalline solid separated and a small amount of oil was removed by treating with absolute ether and decanting. A sample of 3 g. of the crude salt was extracted with 250 cc. of absolute ether in a Soxhlet and after twenty-four hours 2 g. of brucine salt, m. p. 158–159° (cor.), was deposited as a yellow powder.

Anal. Calcd. for $C_{13}H_{15}NO_5 \cdot C_{23}H_{26}N_2O_4$: C, 65.61; H, 6.26; N, 6.36. Found: C, 65.78; H, 6.10; N, 6.43.

Rotation. 0.2 g. made up to 10 cc. with absolute ethanol gave α_D −0.48; *l*, 1; $[\alpha]^{26}D$ −24°. After twenty-four hours there was no evidence of mutarotation.

The brucine salt was found to be much less soluble in absolute ether than its unnitrated analogs. The following procedure was adopted to effect crystallization. A solution of 2.5 g. of salt as obtained was dissolved in 10 cc. of freshly distilled dioxane, 20 cc. of absolute ether was added and the flask kept at 0° for two days. After an additional day at room temperature, lemon-yellow crystals with sharply defined faces, formed. After two additional weeks, small portions of absolute ether being added to make up for evaporation losses, 1.5 g. of large translucent yellow prisms had grown. This fraction, m. p. 145–147° (cor.) had the same rotation and failed to mutarotate. Decomposition of the salt with cold aqueous hydrochloric acid led to optically inactive material.

β-Methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid (V); Brucine Salt.—A solution of 3 g. of the acrylic acid (V) and 4.63 g. of anhydrous brucine in absolute ethanol was warmed on the steam-bath. Following removal of the solvent, 50 cc. of absolute ether was added and the viscous material triturated until a fine powder was formed. A sample of 3 g. of this product, m. p. 115–126° (cor.), was refluxed with 400 cc. of absolute ether and filtered from a small amount of brucine. The solution was kept at 0° for twenty-four hours, whereupon an additional 0.5 g. of brucine was obtained. The solution was filtered, concentrated, seeded, and within forty-eight hours 0.5 g. of the brucine salt, m. p. 132–134° (cor.), was obtained. The salt was analyzed without further crystallization since fresh solvent was found to decompose the salt causing brucine to precipitate. Further low-melting crops could be obtained on concentration of the mother liquors.

Anal. Calcd. for $C_{13}H_{15}ClO_3 \cdot C_{23}H_{26}N_2O_4$: C, 66.60; H, 6.37; N, 4.31. Found: C, 66.76; H, 6.42; N, 4.44.

Rotation. 0.1 g. made up to 5 cc. with absolute ethanol at 22° gave α_D −0.55; *l*, 1; $[\alpha]^{22}D$ −22°. No mutarotation was observed after seventeen hours. Decomposition of all salt fractions with cold aqueous hydrochloric acid gave only inactive acids.

β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-N-acrylylglycine (XII); Brucine Salt.—A solution of 0.7 g. of β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-N-acrylylglycine (XII) and 1 g. of anhydrous brucine in 10 cc. of absolute ethanol was warmed on the steam-bath, then transferred to a breaker and the solvent removed in a vacuum desiccator over calcium chloride at room temperature. On digesting the oily residue with absolute ether, a white powder readily formed, m. p. 152–155° (cor.). The substance was instantaneously soluble in water. On refluxing 1 g. of the crude salt with 600 cc. of absolute ether all went into solution leaving merely a trace of an amorphous solid. Following filtration the solution was concentrated by spontaneous evaporation. After five days the volume had decreased to 200 cc. and 0.45 g. of a white crystalline solid, m. p. 158° (cor.), was obtained (Fraction A). Further concentration to 25 cc. gave 0.2 g. (Fraction B). The residue after complete evaporation was an oily solid.

Anal. Calcd. for $C_{15}H_{19}NO_4 \cdot C_{23}H_{26}N_2O_4$: C, 67.93; H, 6.75; N, 6.25. Found: C, 67.71; H, 6.64; N, 6.36.

Rotation. Fraction A. 0.1 g. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.232; *l*, 1; $[\alpha]^{27}D$ −11.6°. After twelve and a half hours no evidence of mutarotation was observed.

Attempts to liberate the free glycine with cold aqueous hydrochloric acid gave merely oils.

Attempted Resolution of Other Acrylic Acids.—β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (IV) and α,β-dimethyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid (IX) could not be induced to give crystalline alkaloidal salts by the procedures previously described.

Summary

1. 4,5,7-Trimethylcoumarin, prepared from 3,5-dimethylphenol and ethyl acetoacetate, and its 6-nitro and 6-chloro derivatives were hydrolyzed with alkali and methylated to β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid, β-methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid and β-methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid.

2. 3,4,5,7-Tetramethylcoumarin, prepared from 3,5-dimethylphenol and ethyl methylacetoacetate and its 6-nitro and 6-chloro derivatives were hydrolyzed and methylated to α,β-dimethyl-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid, α,β-dimethyl-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid and α,β-dimethyl-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid.

3. Several of these acrylic acids formed alkaloidal salts which were oils, others crystalline salts which dissociated readily. Success attended only the resolution of α,β-dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid. Its half-life was seventy-four minutes in *n*-butanol at 44° and therefore much less than that of α-methyl-β-chloro-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (one hundred and seventy-three minutes). Thus it would appear that in this series of arylacrylic acids, a β-methyl has less effect on the stability than a β-chlorine atom.

4. A discussion of the geometric structure about the double bond of these acrylic acids is given.

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Some New Aminopyrazines and their Sulfanilamide Derivatives

BY JOHN WEIJLARD, MAX TISHLER AND A. E. ERICKSON

It has been established that the introduction of methyl groups into the heterocyclic system of N′ heterocyclic derivatives of sulfanilamides affects chemotherapeutic activity. In some instances the methyl derivatives are superior to the parent drug.[1] The therapeutic importance of 2-sulfanilamidopyrazine (sulfapyrazine)[2] indicates the necessity for the study of the substituted pyrazine-sulfonamides as effective chemotherapeutic agents.

A search of the literature for the requisite alkyl and aryl substituted aminopyrazines revealed that only one such derivative, 2-amino-3,6-dimethylpyrazine (prepared in poor yields by aminating 3,6-dimethylpyrazine with sodamide[3]) seems to be known. Moreover, the recorded methods for preparing aminopyrazine itself are laborious and the yields poor.[4] These processes entail the oxida-

(1) For a recent review of this subject see E. H. Northey, *Ind. Eng. Chem.*, **35**, 829 (1943).

(2) Ellingson, THIS JOURNAL, **63**, 2524 (1941); Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941); Sansville and Spoerri, *ibid.*, **63**, 3153 (1941); Hamburger, Reugsegger, Brookens and Eakin, *Am. J. Med. Sci.*, **204**, 186 (1942).

(3) Chichibabin and Shukina, *J. Russ. Phys.-Chem. Soc.*, **62**, 1189 (1930); Joiner and Spoerri, THIS JOURNAL, **63**, 1929 (1941).

(4) Gabriel and Sonn, *Ber.*, **40**, 4859 (1907); Hall and Spoerri, THIS JOURNAL, **62**, 664 (1940).