Synthesis of some disubstituted naphthazarins

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Some 2,6- and 2,7-disubstituted naphthazarins have been synthesized by cyclizing the corresponding β-(2,5-dimethoxybenzoyl)-acrylic acids. With one exception, it was established that isomerization does not occur and therefore that the method provides unambiguous proof of structure for these naphthazarins. Conversely, the procedure was used to determine the positions of the chlorine atoms in two β-(2,5-dimethoxybenzoyl)-chloroacrylic acids.

Quelques naphtazarines 2,6- et 2,7-disubstituées ont été préparées par cyclisation des acides β-(2,5-diméthoxybenzoyl)-acryliques correspondants. A une exception près, nous avons pu établir que les substances ne s'isomérisent pas au cours de la réaction. La méthode permit donc de déterminer la structure des naphtazarines ainsi préparées et inversement la position de l'atome de chlore dans deux acides β-(2,5-diméthoxybenzoyl)-chloracryliques.

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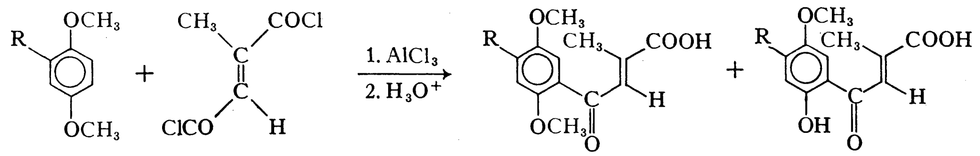
Several facile and versatile methods are available for the preparation of naphthazarins (1–4); of these, the Zahn and Ochwat method (2) and the Brockmann and Mueller modification (5) of it have proven to be the most satisfactory on the basis of both ease of operation and availability of starting materials. It is therefore not surprising that this condensation of hydroquinones or their ethers with maleic anhydrides has been used frequently. However, when each of the reacting substrates carries a substituent (or two different ones), it becomes difficult to establish the relative positions of these groups.

The only known condensation product of hydroxyhydroquinone and citraconic anhydride has been described simply as 2-methyl-6(or 7)-hydroxynaphthazarin (6). Kuroda (7) obtained two products from the condensation of toluhydroquinone with citraconic anhydride; the lower melting substance was also obtained by Brockmann and Mueller (5). The higher melting product was later recognized as the 2,6-dimethyl isomer, and 2,6-dichloronaphthazarin was synthesized by the use of Roussin's method (8). Recently (9, 10), 2,6-dimethoxynaphthazarin was obtained by the same method, and the structures of the 2,7-dimethoxy isomer and 2-methoxy-6- and -7-hydroxynapthazarins were deduced from it.

It was thought advisable, in view of the remaining uncertainties and of the number of naturally occurring naphthazarins, to seek general and facile methods of establishing the structures of the compounds obtained by the one-step condensation of Zahn and Ochwat. Indeed, Roussin's method, repeatedly used to date (not to speak of the tedious elaboration of the molecule (11–13)), is quite limited in scope as a result of the unavailability of the required 1,5-dinitronaphthalenes. The procedure chosen consisted of the preparation and cyclization of isomeric *trans*-β-(2,5-dimethoxybenzoyl)-acrylic acids, since the parent compound had been shown to yield naphthazarin under appropriate conditions (14). The required *trans*-β-(2,5-dimethoxybenzoyl)-α- and -β-methylacrylic acids were prepared by methods devised for the *p*-bromobenzoyl derivatives (15) (Reaction Schemes 1 and 2). In two cases isomeric products were encountered: VI instead of XIV and VIII instead of XVI. Compound XIV was eventually obtained by decreasing the amount of $AlCl_3$, but acid XVI could not be synthesized.

From the reaction of chloromaleic anhydride and 2,5-dimethoxytoluene two substances (among others) were isolated which, according to their color, spectra, analyses, and method of preparation (16), were thought to be the corresponding *cis*-β-benzoyl-β-chloro- and *trans*(?)-β-benzoyl-α-chloro-acrylic acids. The *cis* acid is cyclic in the solid state ($\lambda^{KBr}_{\text{lactone C=O}}$ 5.7 μ) and is

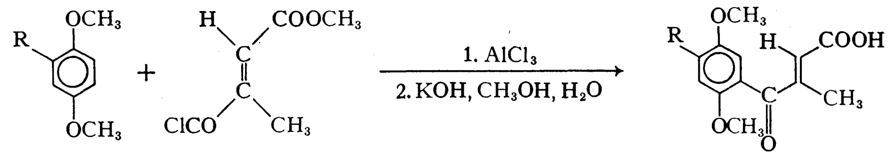


I $R = H$
II $R = CH_3$
III $R = Cl$
IV $R = OCH_3$

V $R = H$
VI $R = CH_3$
VII $R = Cl$
VIII $R = OCH_3$

IX $R = H$
X $R = CH_3$
XI $R = Cl$
XII $R = OCH_3$

Reaction Scheme 1.



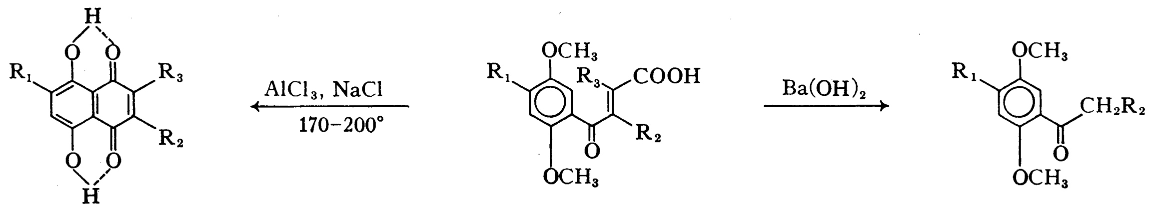
I, II, III, IV

XIII $R = H$
XIV $R = CH_3$
XV $R = Cl$
XVI $R = OCH_3$

Reaction Scheme 2.

converted with relative ease into the corresponding naphthazarin (42%), whereas the *trans*(?) acid is only difficultly cyclized (6%), in agreement with other *trans* acids.

The naphthazarins of unknown or unconfirmed structure were prepared by the Brockmann and Mueller method (5), and in all cases mixtures of the 2,6- and 2,7-disubstituted isomers were obtained and separated by fractional crystallization. These isomers were then compared with the naphthazarins obtained from the corresponding *trans*-β-benzoylacrylic acids (Reaction Scheme 3). (In view of recently reported isomerizations (10) during condensations of this type, the need arises for rigid proof of the structure of each isomer.) Both *trans*-β-(2,5-dimethoxy-4-substituted-benzoyl)-α- and -β-methylacrylic acids were cyclized in the same manner as the parent compound (14); since each acid, with one exception, gave only one naphthazarin without a detectable amount of the other isomer, the relative positions of the substituents in the two isomers are established. (It is scarcely conceivable that each one of a pair of isomeric acids would isomerize in opposite directions.)



XXV $R_1 = R_2 = H, R_3 = CH_3$
XXVI $R_1 = R_3 = CH_3, R_2 = H$
XXVII $R_1 = Cl, R_2 = H, R_3 = CH_3$
XXVIII $R_1 = OH, R_2 = H, R_3 = CH_3$
XXIX $R_1 = R_2 = CH_3, R_3 = H$
XXX $R_1 = Cl, R_2 = CH_3, R_3 = H$
XXXI $R_1 = OH, R_2 = CH_3, R_3 = H$

V $R_1 = R_2 = H, R_3 = CH_3$
VI $R_1 = R_3 = CH_3, R_2 = H$
VII $R_1 = Cl, R_2 = H, R_3 = CH_3$
VIII $R_1 = OCH_3, R_2 = H, R_3 = CH_3$
XIII $R_1 = R_3 = H, R_2 = CH_3$
XIV $R_1 = R_2 = CH_3, R_3 = H$
XV $R_1 = Cl, R_2 = CH_3, R_3 = H$
XVI $R_1 = OCH_3, R_2 = CH_3, R_3 = H$

XVII $R_1 = R_2 = H$
XVIII $R_1 = CH_3, R_2 = H$
XIX $R_1 = Cl, R_2 = H$
XX $R_1 = OCH_3, R_2 = H$
XXI $R_1 = H, R_2 = CH_3$
XXII $R_1 = R_2 = CH_3$
XXIII $R_1 = Cl, R_2 = CH_3$
XXIV $R_1 = OCH_3, R_2 = CH_3$

Reaction Scheme 3.

The preparation of 2-methyl-6- and -7-hydroxynaphthazarins caused considerable difficulty. A number of suitable substrates were prepared: *cis*-(2,4,5-trimethoxybenzoyl)-β-methylacrylic acid, 2,4,5-trimethoxybenzoyl)-α- and -β-methylpropionic acids, and α-carboxy-β-(2,4,5-trimethoxybenzoyl)-β-methylacrylic acid. All of these intermediates and *trans*-β-(2,4,5-trimethoxybenzoyl)-α-methylacrylic acid gave the same naphthazarin upon cyclization. Eventually this compound was found to be the 2,6 isomer. The one-step synthesis from trimethoxybenzene and citraconic anhydride, however, gave a mixture of both isomers. Both 2-methyl-6- and -7-hydroxynaphthazarins were obtained after substitution of chlorine by KOH on 2-methyl-6- and -7-chloronaphthazarins.

Upon cyclization in the usual way, the *cis*-β-2,5-dimethoxy-4-methylbenzoyl-β-chloroacrylic acid yielded only 2-methyl-6-chloronaphthazarin, whereas the corresponding *trans*(?)-α-chloroacrylic acid gave 2-methyl-7-chloronaphthazarin. It was thus established that the positions of the chlorine atoms had been postulated correctly.

The structures of the β-benzoyl-α- and -β-methylacrylic acids were unequivocally confirmed by barium hydroxide catalyzed, retro-aldol degradations of the side chains, followed by comparison of the resulting acetophenones and propiophenones with authentic compounds (Reaction Scheme 3). The partially demethylated acids (IX–XI) do not yield ketones upon steam-distillation with barium hydroxide but are converted into oxygen-ring compounds (these results will be submitted for publication shortly). The structures of these hydroxy acids can be verified (see Experimental) by etherification to the corresponding dimethoxy acids (V–VIII) if it is assumed that the ether group ortho to the carbonyl function has been cleaved selectively, as is well established in numerous cases. 1,2,4-Trimethoxybenzene, on the other hand, gives rise to a dihydroxy acid; the hydroxy groups are tentatively assigned to positions 2 and 4 on similar grounds.

DISCUSSION

The *trans*-β-benzoyl-α-methylacrylic acids (V–XI) show two well-defined absorption bands of comparable intensity (log ε ~4.0) in the 220–280 mμ region. With the exception of VIII, the position of these bands does vary appreciably within the group of compounds studied. However, a hypsochromic shift of about 10 mμ is noted for the band at higher wavelengths for the corresponding β-methyl acids (XIII–XV). A considerable hypochromic effect is also noted which is not shown by simple β-benzoylacrylic acid (17). The shapes of the two-component bands obtained for the β-methyl acids are similar to those expected for an intensity ratio of approximately 1:2 (18), and probably denote considerable out-of-place twisting of the carbonyl group.

In the case of naphthazarins, several useful correlations can be made. All 2,6-disubstituted naphthazarines have melting points considerably higher (40–100°) than those of the 2,7 isomers. No significant difference between the isomers can be detected in the ultraviolet spectra, except that the molar absorptivity is slightly but consistently higher for the 2,6 isomers. It has been reported (9) that the hydroxylic protons of 2,7-dimethoxynaphthazarin show nonequivalent chemical shifts in the nuclear magnetic resonance spectrum and that they become equivalent in the 2,6 isomers. These characteristics have now been noted for the corresponding dichloro and dimethyl compounds.

EXPERIMENTAL

All melting points are corrected and were taken in capillary tubes (Thomas–Hoover apparatus). The infrared spectra were recorded with a Perkin–Elmer infracord spectrophotometer, and the ultraviolet spectra with a Beckman DK-1A spectrophotometer. The nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer, tetramethylsilane being used as an internal reference.

Preparation of Acetophenones and Propiophenones (XVII–XXIV)

Acetyl chloride or propionyl chloride (0.1 mole) was added dropwise to a stirred mixture of each of the 2,5-dimethoxybenzenes (I–IV) (0.1 mole), aluminium chloride (0.2 mole), and CS_2 (25 ml) at room temperature. After the solution was stirred for 3 h, the complex was decomposed in the usual way with ice and hydrochloric acid, and the ketones were dissolved in ether. The ethereal solution was extracted with a 5% NaOH solution to remove demethylated ketones, which were discarded. The required ketones were then crystallized from a mixture of benzene and petroleum ether (b.p. 60–90°). The liquid 2,5-dimethoxyaceto- and 2,5-dimethoxypropio-phenones were steam-distilled until free from starting material, and portions were converted into the semicarbazones: 2,5-dimethoxyacetophenone (XVII) (82%), semicarbazone, m.p. 187–188° (lit. m.p. 181–182° (19)); 2,5-dimethoxypropiophenone (XXI) (64%), semicarbazone, m.p. 192–193° (lit. m.p. 191–192° (20)); 2,5-dimethoxy-4-methylacetophenone (XVIII) (52%), m.p. 74.5–75.5° (lit. m.p. 74° (21)); 2,5-dimethoxy-4-methylpropiophenone (XXII) (75%), m.p. 76–77° (Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75; Found: C, 69.13; H, 7.95); 2,5-dimethoxy-4-chloroacetophenone (XIX) (82%), m.p. 98–99° (lit. m.p. 100.0–102.5° (22)); 2,5-dimethoxy-4-chloropropiophenone (XXIII) (50%), m.p. 80–81° (Anal. Calcd. for $C_{11}H_{13}O_3Cl$: C, 57.77; H, 5.73; Cl, 15.51; Found: C, 57.89; H, 5.79; Cl, 15.67); 2,4,5-trimethoxyacetophenone (XX) (58%), m.p. 97–98° (lit. m.p. 99° (23)); 2,4,5-trimethoxypropiophenone (XIV) (60%), m.p. 108–109° (lit. m.p. 106–108° (24)).

Retro-aldol Degradation of trans-β-(2,5-Dimethoxybenzoyl)-α- and -β-methylacrylic Acids

Each of the *trans*-β-(2,5-dimethoxybenzoyl)-α- and -β-methylacrylic acids (0.5 g) was dissolved in a mixture of barium hydroxide (1.5 g) and water (15 ml), and steam was passed through the solution until the ketone was no longer carried over. 2,4,5-Trimethoxyaceto- and 2,4,5-trimethoxypropio-phenones were not volatile and were recovered from the reaction flask. The ketones were identified by mixture melting points with the compounds prepared above.

Reaction of 1,4-Dimethoxybenzenes with Mesaconyl Chloride

Mesaconyl chloride (0.075 mole) was added dropwise over a period of 1 h to a well-stirred mixture of each of the 1,4-dimethoxybenzenes (0.112 mole) (I–IV), $AlCl_3$ (0.15 mole), and CS_2 (50 ml) at 35°. Stirring was continued at the same temperature for 3 h. The reaction mixture was then cooled and the complex decomposed in the usual way with ice and hydrochloric acid. After the solution was allowed to stand overnight, the products were dissolved in ether. The ethereal solution was washed with water and extracted with a 5% solution of $NaHCO_3$, to which acetic acid was added until precipitation was complete. The precipitate, consisting mainly of the corresponding *trans*-β-(2,5-dimethoxybenzoyl)-α-methylacrylic acid (V–VIII), was filtered off and the filtrate acidified strongly with concentrated HCl. After the solution was cooled, a mixture of the abovementioned acid and the corresponding 2-hydroxy acid (IX–XII) was obtained; this could be separated easily by fractional crystallization.

trans-β-(2,5-Dimethoxybenzoyl)-α-methylacrylic Acid (V) and trans-β-(2-Hydroxy-5-methoxybenzoyl)-α-methylacrylic Acid (IX)

Compound V crystallized from 50% ethanol or benzene as yellow needles (2.8 g, 15%), m.p. 146–147°; $\lambda_{max}^{CHCl_3}$ 5.89, 6.04, 6.22 μ; λ_{max}^{EtOH} 221 mμ (log ε 4.11), 257 mμ (log ε 4.06).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.21; H, 5.61.

When this substance was steam-distilled with $Ba(OH)_2$, 2,5-dimethoxyacetophenone was obtained. Semicarbazone, m.p. and mixture m.p. 187–188°.

After the solvent was decanted from compound V, compound IX crystallized in red flakes, m.p. 150.5–151.0° (1.4 g, 8%); $\lambda_{max}^{CHCl_3}$ 5.86, 6.06, 6.20 μ; λ_{max}^{EtOH} 226 mμ (log ε 4.04), 264 mμ (log ε 4.07).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.05; H, 5.14.

Etherification of this substance with dimethyl sulfate and KOH yielded compound V.

trans-β-(2,5-Dimethoxy-4-methylbenzoyl)-α-methylacrylic Acid (VI) and trans-β-(2-Hydroxy-4-methyl-5-methoxybenzoyl)-α-methylacrylic Acid (X)

Compound VI crystallized from 50% acetic acid as yellow needles, m.p. 196–197° (4.8 g, 24%); λ_{max}^{EtOH} 229 mμ (log ε 4.09), 258 mμ (log ε 4.03).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.85; H, 6.28.

Steam-distillation with $Ba(OH)_2$ gave 2,5-dimethoxy-4-methylacetophenone, m.p. 74.5–75.5°, mixture m.p. 75–76°.

Compound X was obtained as orange flakes by cooling the mother liquor of the preceding crystallization, m.p. 136.5–137.5° (1.3 g, 7%); λ_{max}^{EtOH} 230 mμ (log ε 3.96), 274 mμ (log ε 4.04).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.28; H, 5.41.

Etherification of this substance with dimethyl sulfate and KOH gave compound VI.

trans-β-(2,5-Dimethoxy-4-chlorobenzoyl)-α-methylacrylic Acid (VII) and trans-β-(2-Hydroxy-4-chloro-5-methoxybenzoyl)-α-methylacrylic Acid (XI)

Compound VII crystallized from methanol as yellow needles, m.p. 201–202° (decomp.) (5.1 g, 24%); λ_{max}^{EtOH} 227 mμ (log ε 4.02), 257 mμ (log ε 3.90).

Anal. Calcd. for $C_{13}H_{13}O_5Cl$: C, 54.84; H, 4.60; Cl, 12.45. Found: C, 54.80; H, 4.65; Cl, 12.22.

Steam-distillation of this substance with $Ba(OH)_2$ gave 2,5-dimethoxy-4-chloroacetophenone, m.p. and mixture m.p. 97.5–98.5°.

By diluting the mother liquor of the preceding crystallization with water, compound XI was obtained as orange needles, m.p. 142–143° (1.5 g, 7%); λ_{max}^{EtOH} 228 mμ (log ε 4.01), 271 mμ (log ε 4.12).

Anal. Calcd. for $C_{12}H_{11}O_5Cl$: C, 53.25; H, 4.10; Cl, 13.11. Found: C, 53.00; H, 4.24; Cl, 13.02.

Etherification of this substance in the usual way yielded compound VII.

trans-β-(2,4,5-Trimethoxybenzoyl)-α-methylacrylic Acid (VIII)

The foregoing general method gave only a 2% yield of compound VIII. However, by using a mixture of nitrobenzene (50 ml) and tetrachloroethane (50 ml) as solvent and by lowering the reaction temperature to 20°, the substance was obtained as yellow needles from 60% ethanol, m.p. 196–197° (5.4 g, 26%); $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ε 4.14), 252 mμ (sh).

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.89; H, 5.66.

The usual Ba(OH)$_2$ degradation yielded 2,4,5-trimethoxyacetophenone, m.p. and mixture m.p. 97.0–97.5°.

Compound XII was not obtained by either of the foregoing methods. However, when the original procedure was followed, a 1% yield of an acid was obtained which was assumed to be *trans*-β-(2,4-dihydroxy-5-methoxybenzoyl)-α-methylacrylic acid on the basis of the analysis and the predictably easy cleavage of the ether groups, m.p. 181.0–182.5° (yellow needles); $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ε 3.97), 276 mμ (log ε 3.92).

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.07; H, 4.74.

Reaction of 1,4-Dimethoxybenzenes with trans-α-Methyl-β-carbomethoxyacrylyl Chloride

A quantity of 7.2 g (0.05 mole) of *trans*-α-methyl-β-carbomethoxyacrylic acid, m.p. 51° (lit. m.p. 52° (25)), was converted into the acid chloride (15) and added dropwise to a well-stirred mixture of each of the 1,4-dimethoxybenzenes (0.10 mole) (I–IV), AlCl$_3$ (0.3 mole), and CS$_2$ (50 ml) at 35°. Stirring was continued for 3 h at the same temperature. The reaction mixture was then cooled, decomposed in the usual way, and extracted with ether. After evaporation of the ether, the residue was added to a mixture of methanol (120 ml), water (60 ml), and KOH (6.0 g), which was then stirred for 18 h at room temperature, diluted with water (300 ml), and extracted with ether. The *trans*-β-(2,5-dimethoxybenzoyl)-β-methylacrylic acids (XIII–XV) were then obtained by precipitation with concentrated HCl.

trans-β-(2,5-Dimethoxybenzoyl)-β-methylacrylic Acid (XIII)

Compound XIII crystallized from 50% ethanol as yellow needles, m.p. 124–125° (4.9 g, 39%); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 3.33, 5.90, 6.02, 6.10 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 228 mμ (log ε 4.28), 247 mμ (sh).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.33; H, 5.59.

Upon steam-distillation with Ba(OH)$_2$, 2,5-dimethoxypropiophenone was obtained. Semicarbazone, m.p. 192–193.5°, mixture m.p. 191–193°.

trans-β-(2,5-Dimethoxy-4-methylbenzoyl)-β-methylacrylic Acid (XIV)

Compound XIV, prepared at room temperature, crystallizes from 60% ethanol as yellow needles, m.p. 170–171° (5.6 g, 42%); $\lambda_{\max}^{\mathrm{EtOH}}$ 229 mμ (log ε 4.11), 247 mμ (sh). Steam-distillation of this substance with Ba(OH)$_2$ yielded 2,5-dimethoxy-4-methylpropiophenone, m.p. and mixture m.p. 76–77°.

trans-β-(2,5-Dimethoxy-4-chlorobenzoyl)-β-methylacrylic Acid (XV)

Compound XV crystallized from 50% ethanol as yellow needles, m.p. 178–179° (3.1 g, 22%); $\lambda_{\max}^{\mathrm{EtOH}}$ 229 mμ (log ε 4.12), 246 mμ (sh).

Anal. Calcd. for $C_{13}H_{13}O_5Cl$: C, 54.84; H, 4.60; Cl, 12.45. Found: C, 55.05; H, 4.78; Cl, 12.32.

When this substance was steam-distilled with Ba(OH)$_2$, 2,5-dimethoxy-4-chloropropiophenone was obtained, m.p. and mixture m.p. 79.5–80.5°.

cis-β-(2,4,5-Trimethoxybenzoyl)-β-methylacrylic Acid

To a mixture of 1,2,4-trimethoxybenzene (0.10 mole) and AlCl$_3$ (0.11 mole) in methylene chloride (30 ml) at 35–40° was added dropwise citraconic anhydride (0.05 mole); stirring was continued at the same temperature for 5 h. After hydrolysis, the product was dissolved in ether and the ethereal solution extracted with a 5% solution of NaHCO$_3$. Acidification of the extract with concentrated HCl gave *cis*-β-(2,4,5-trimethoxybenzoyl)-β-methylacrylic acid (4.9 g, 35%), m.p. 139–140° (colorless needles when crystallized from 50% ethanol). The compound failed to react with an aqueous solution of Ba(OH)$_2$, and reacted slowly with a solution of KMnO$_4$ in acetone; $\nu_{\max}^{\mathrm{KBr}}$ 1 743, 1 723 (sh), 1 653 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.08; H, 5.65.

β-(2,4,5-Trimethoxybenzoyl)-butyric Acid

A mixture of 1.0 g of *cis*-β-(2,4,5-trimethoxybenzoyl)-β-methylacrylic acid, 4.25 g of sodium hydrosulfite, 20 ml of ethanol, and 5 ml of water was refluxed for 30 min, cooled, filtered, and evaporated under a vacuum. The residue was dissolved in a 5% solution of NaHCO$_3$ and filtered. Acidification with HCl yielded β-(2,4,5-trimethoxybenzoyl)-butyric acid, m.p. 130.0–131.5° (crystallized from benzene and petroleum ether); $\lambda_{\max}^{\mathrm{EtOH}}$ 232 mμ (log ε 4.18), 268 mμ (log ε 3.92). The compound is identical with the known substance prepared according to Hardegger *et al.* (12), m.p. and mixture m.p. 129.5–131° (lit. 128–129°).

β-(2,4,5-Trimethoxybenzoyl)-α-methylpropionic Acid

This compound (colorless losanges from 50% ethanol) was prepared, in the same way as the preceding substance, from *trans*-β-(2,4,5-trimethoxybenzoyl)-α-methylacrylic acid, m.p. 164–165°; $\lambda_{\max}^{\mathrm{EtOH}}$ 232 mμ (log ε 3.93), 268 mμ (log ε 3.73).

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.81; H, 6.55.

cis-β-(2,5-Dimethoxy-4-methylbenzoyl)-β-chloroacrylic Acid and trans(?)-β-(2,5-Dimethoxy-4-methylbenzoyl)-α-chloroacrylic Acid

A quantity of 13.3 g (0.10 mole) of chloromaleic anhydride was added dropwise to a well-stirred mixture of 30.4 g (0.20 mole) of 2,5-dimethoxytoluene, 26.6 g (0.20 mole) of AlCl$_3$, and 100 ml of CS$_2$ at room temperature. The reaction mixture was stirred for several hours, allowed to stand overnight, and then decomposed in the usual way. The products were dissolved in ether and the ethereal solution was extracted with a 5% NaHCO$_3$ solution. Acidification with AcOH gave *cis*-β-(2,5-dimethoxy-4-methylbenzoyl)-β-chloroacrylic acid, colorless plates when crystallized from 60% ethanol, m.p. 159–160° (12.0 g, 42%); $\lambda_{\max}^{\mathrm{EtOH}}$ 269 mμ (log ε 3.79).

Anal. Calcd. for $C_{13}H_{13}O_5Cl$: C, 54.84; H, 4.60; Cl, 12.45. Found: C, 54.96; H, 4.73; Cl, 12.35.

Addition of concentrated HCl to the filtrate gave a mixture of compounds from which *trans*(?)-β-(2,5-dimethoxy-4-methylbenzoyl)-α-chloroacrylic acid could be isolated by fractional crystallization, yellow needles when crystallized from 50% ethyl alcohol, m.p. 209° (decomp.) (0.9 g, 3%); $\lambda_{\max}^{\mathrm{EtOH}}$ 227 mμ (log ε 4.09), 266 mμ (log ε 3.99).

Anal. Calcd. for $C_{13}H_{13}O_5Cl$: C, 54.84; H, 4.60; Cl, 12.45. Found: C, 55.01; H, 4.86; Cl, 12.35.

Cyclization of the β-(2,5-Dimethoxybenzoyl)-acrylic Acids

To a molten mixture of $AlCl_3$ (10.0 g) and NaCl (2.0 g) at 170° was added 1.0 g of the powdered benzoylacrylic acid. The melt was stirred and the temperature raised to 200° for 3 min. The complex was then allowed to cool and was decomposed in the usual way. The naphthazarin was extracted with benzene. After evaporation of the solvent, the crude substance was crystallized from either acetone (for the 2,6 isomers) or petroleum ether (b.p. 60–90°) (for the 2- and 2,7-substituted compounds).

Methylnaphthazarin (XXV), m.p. 170–172° (lit. m.p. 173° (26)), was obtained from V (9%) and from XIII (20%); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.16, 6.31 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 277 mμ (log ε 3.84).

2,7-Dimethylnaphthazarin (XXVI) (80 mg, 10%), m.p. 125–127°, was obtained from VI; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.22, 6.36 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 282 mμ (log ε 3.92); nuclear magnetic resonance C_5—OH and C_8—OH, δ 12.50 and 12.97 ($CDCl_3$).

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.25; H, 4.56.

This compound has previously been reported as 2,6- or 2,7-dimethylnaphthazarin (lit. m.p. 127° (5, 7)).

2,6-Dimethylnaphthazarin (XXIX) (60 mg, 7%), m.p. 224° (no m.p. decomp. >200° (8)), was obtained from XIV; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.22, 6.37 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 282 mμ (log ε 2.95); nuclear magnetic resonance C_5—OH and C_8—OH, δ 12.78 ($CDCl_3$).

Anal. Found: C, 66.32; H, 4.60.

2-Methyl-7-chloronaphthazarin (XXVII) (105 mg, 13%), m.p. 146.0–147.5°, was obtained from VII (38 mg, 9%) and from *trans*(?)-β-(2,5-dimethoxy-4-methylbenzoyl)-α-chloroacrylic acid; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.20, 6.39 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 293 mμ (log ε 3.91).

Anal. Calcd. for $C_{11}H_7O_3Cl$: C, 55.36; H, 2.96; Cl, 14.86. Found: C, 55.19; H, 2.93; Cl, 14.52.

2-Methyl-6-chloronaphthazarin (XXX) (50 mg, 6%), m.p. 226–227°, was obtained from XV (350 mg, 42%) and from *cis*-β-(2,5-dimethoxy-4-methylbenzoyl)-β-chloroacrylic acid; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.20, 6.38 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 292 mμ (log ε 3.96).

Anal. Found: C, 55.09; H, 3.04; Cl, 14.71.

2-Methyl-7-hydroxynaphthazarin (XXVIII)

A solution of 2-methyl-7-chloronaphthazarin (XXVII) (0.3 g) and KOH (0.4 g) in 50 ml of 60% ethanol was refluxed until the original blue color turned red. Compound XXVIII was then isolated in the usual way, m.p. 164–166°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.25, 6.38 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 302 mμ (log ε 3.85).

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.78; H, 3.73.

Etherification with dimethyl sulfate and K_2CO_3 in acetone gave 2-methyl-7-methoxynaphthazarin, m.p. 174.5–175.5°.

2-Methyl-6-hydroxynaphthazarin (XXXI)

Compound XXXI was the only isomer isolated from the cyclization of VIII (4%), of *cis*-β-(2,4,5-trimethoxybenzoyl)-β-methylacrylic acid (11%), of β-(2,4,5-trimethoxybenzoyl)-butyric acid (11%), of β-(2,4,5-trimethoxybenzoyl)-α-methylacrylic acid, and of β-(2,4,5-trimethoxybenzoyl)-β-methyl-α-carboxybutyric acid (11%), m.p. 201–202°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.25, 6.39 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 302 mμ (log ε 3.90).

Anal. Found: C, 60.14; H, 3.71.

This compound has previously been reported as 2-methyl-6-(or 7)-hydroxynaphthazarin (lit. m.p. 202° (6)). Etherification in the foregoing way yielded 2-methyl-6-methoxynaphthazarin, m.p. 222.0–223.5°.

One-Step Preparations of 2,6- and 2,7-Disubstituted Naphthazarins

A mixture of one of the 2-substituted 1,4-dimethoxybenzenes (2.0 g) and either citraconic or chloromaleic anhydride (10.0 g) was added to a molten mixture of $AlCl_3$ (20.0 g) and NaCl (5.6 g) at 170°. The reaction mixture was stirred for 2–3 min, cooled, and decomposed in the usual way. The naphthazarins were isolated as previously indicated. The 2,6 isomers were separated by crystallization from acetone, and the 2,7 isomers were obtained by addition of petroleum ether (b.p. 60–90°) to the mother liquor. Mixtures of these two isomers were always obtained, and no 2,3- or poly-substituted naphthazarins were detected. In all cases, the identities of the naphthazarins were established by their mixture melting points with the above-mentioned authentic samples.

Reaction of 1,4-Dimethoxy-2-chlorobenzene with Chloromaleic Anhydride

This reaction was carried out and the two isomeric naphthazarins were separated as indicated above. 2,7-Dichloronaphthazarin, m.p. 174.0–175.5°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.16, 6.31, 6.40 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 293 mμ (log ε 3.91); nuclear magnetic resonance C_5—OH and C_8—OH, δ 12.33 and 12.70 ($CDCl_3$).

Anal. Calcd. for $C_{10}H_4O_4Cl_2$: C, 46.36; H, 1.56; Cl, 27.37. Found: C, 46.29; H, 1.53; Cl, 27.37.

2,6-Dichloronaphthazarin, m.p. 242–244° (decomp. ca. 240°) (8); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.16, 6.30, 6.40 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 292 mμ (log ε 3.96); nuclear magnetic resonance C_5—OH and C_8—OH, δ 12.53 ($CDCl_3$).

Anal. Found: C, 46.59; H, 1.60; Cl, 27.44.

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