213. Reactions with Benzo[*b*]thiophene-2,3-diones I: Synthesis of 2,3-Dihydroxy-2,3-diaryl(aralkyl)benzo[*b*]thiophene Derivatives

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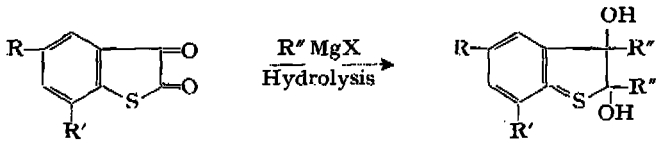
Summary. Benzo[*b*]thiophene-2,3-diones (**1**) react with *Grignard* reagents to yield 2,3-dihydroxy-2,3-diaryl(aralkyl)benzo[*b*]-thiophenes (**2**). The latter compounds yield 3,3-diaryl(aralkyl)-benzo[*b*]thiophene-2-ones (**3**) by pinacolone rearrangement. Treatment of **3** by hot ethanolic sodium hydroxide solution yields the corresponding carboxylic acids by hydrolytic heteroring opening.

For a continuing investigation of the biological activity of benzo[*b*]thiophene derivatives, 2,3-dihydroxy-2,3-diaryl(aralkyl) and 2-oxo-3,3-diaryl(aralkyl) derivatives were required. The reaction of benzo[*b*]thiophene-2,3-diones (**1**) with *Grignard* reagents and subsequent rearrangement of the resulting pinacols seemed to be a possible simple route for their synthesis. Surprisingly, these reactions have not been reported for **1**, although the analogous reactions with isatin [1], N-alkylisatin [2] [3], and benzo[*e*]coumaran-2,3-dione [4] have been described.

The compounds **1a–1c** reacted with *Grignard* reagents, namely, phenylmagnesium bromide and benzylmagnesium chloride, and yielded colourless products, the analytical data of which were in good agreement with the expected pinacol structures **2**. The IR. spectrum of **2a** showed two strong bands at 3350 and 3740 cm^{-1}, indicating the presence of two hydroxyl groups. Attempts to control the addition of the reagent to one carbonyl group only were unsuccessful.



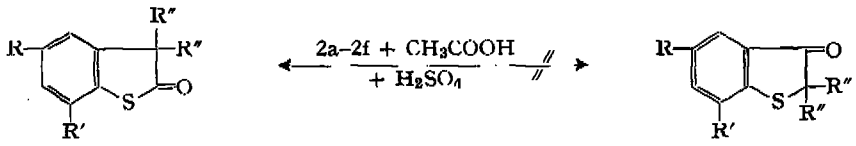
1a R = R′ = H
1b R = CH_3, R′ = H
1c R = H, R′ = CH_3

2a R = R′ = H, R″ = C_6H_5
2b R = R′ = H, R″ = $CH_2C_6H_5$
2c R = CH_3, R′ = H, R″ = C_6H_5
2d R = CH_3, R′ = H, R″ = $CH_2C_6H_5$
2e R = H, R′ = CH_3, R″ = C_6H_5
2f R = H, R′ = CH_3, R″ = $CH_2C_6H_5$

The isolation of **2a–2f** in good yields is in accordance with the behaviour of benzo[*e*]coumaran-2,3-dione [4], and in contrast with the behaviour of isatin [2] and N-alkylisatin [3], towards the same reagent.

When the 2,3-diols **2a–2f** were heated with glacial acetic acid in the presence of concentrated sulfuric acid, colourless products were obtained in good yields presenting the analytical data of the expected pinacolone rearrangement products for which two structures, **3** and **4**, seemed possible. Taking into consideration the relative stability of the carbenium ion resulting by the accepted mechanism for the removal of a protonated hydroxyl group from positions 2 or 3 in compound **2**, it is quite

Possibilities of pinacolone rearrangement of compound **2**



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3a R = R′ = H, R″ = C_6H_5
3b R = R′ = H, R″ = $CH_2C_6H_5$
3c R = CH_3, R′ = H, R″ = C_6H_5
3d R = CH_3, R′ = H, R″ = $CH_2C_6H_5$
3e R = H, R′ = CH_3, R″ = C_6H_5
3f R = H, R′ = CH_3, R″ = $CH_2C_6H_5$

reasonable to assume that this removal would lead to the formation of compounds **3** rather than **4**. This proposal finds support from the analogy to the behaviour of structurally related heterocyclic diols, namely, 2,3-dihydroxy-2,3-diarylbenzo[*e*]-coumaran (**5**) on rearrangement under similar conditions [4]. Moreover, the pina-

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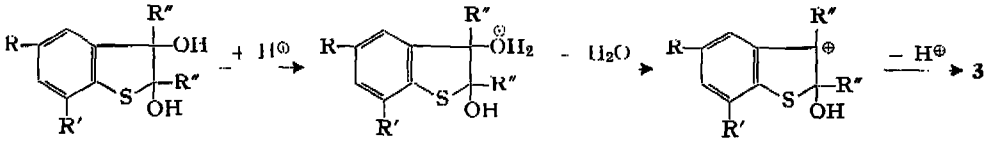
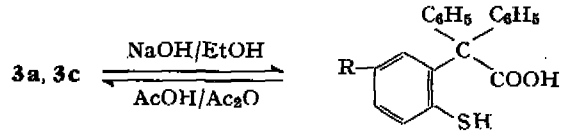
colone rearrangement products of **2a–2f** exhibited absorption at 1670 cm^{-1} characteristic for γ-thiolactones. (The alternative structure **4** would necessitate the presence of a carbonyl absorption at higher frequency for an unconjugated carbonyl function in a five membered heterocycle [5]).



An independant chemical proof for this structural proposal was tried depending on the relative reactivity of the carbonyl groups in positions 2 and 3 in benzo[*b*]thiophene-2,3-diones [6], and in analogy to the behaviour of isatin [7]. Reaction of

compound **1b** with benzene in presence of concentrated sulfuric acid under the same experimental conditions yielded effectively **3c** identified by melting and mixed melting points.

Treatment of **3a** and **3c** with hot ethanolic sodium hydroxide gave the triphenylacetic acid derivatives **6a** and **6b** by heteroring opening, respectively. This behaviour is in contrast to the reported formation of 1-benzhydryl-2-naphthol on attempted hydrolysis of 3,3-diphenylbenzo[*e*]coumaran-2-one under the same experimental conditions [4]. The structures proposed for compounds **6a** and **6b** were supported by analytical data, IR. absorption bands corresponding to the mercaptan and carboxylic groups, and the fact that they are soluble in cold aqueous sodium carbonate and are reprecipitated on acidification. Moreover, **6a** was lactonised easily into the starting pinacolone **3a** by the action of acetic anhydride.



6a R = H; **6b** R = CH_3

Experimental

The melting points are uncorrected. IR. spectra were obtained in KBr on a *Perkin-Elmer* spectrophotometer Infracord 137.

Action of Phenyl and Benzylmagnesium Halides on Benzo[b]*thiophene-2,3-diones* (**1a–1c**). To a cold *Grignard* solution (prepared from 1.0 g of magnesium and the appropriate quantity of the halide in 150 ml of dry ether) was added dropwise while stirring a cold solution of 2.0 g of each compound **1a–1c** in about 50 ml of dry benzene. After about 30 min, about 100 ml of saturated aqueous ammonium chloride solution with 2 ml of concentrated hydrochloric acid were added. After separation of the ethereal layer, the aqueous layer was extracted twice each with 25 ml ether. The combined ethereal solution was washed with 50 ml cold water, then evaporated on a warm water bath. The residue was washed with petroleum ether (b.p. 40–60°), and crystallized from benzene/benzine.

Table 1. Grignard *Products* (**2**) *from Benzo*[b]*thiophene-2,3-diones* (**1**)

Grignard product	m.p. °C	Yield %	Formula	Calc. Found	Analysis % C	H	S
2a	141	85	$C_{20}H_{16}O_2S$		75.08	4.96	10.10
					74.99	5.03	10.00
2b	165	90	$C_{22}H_{20}O_2S$		75.90	5.70	9.20
					75.84	5.19	9.20
2c	179	88	$C_{21}H_{18}O_2S$		75.43	5.43	9.60
					75.80	5.20	9.62
2d	145	92	$C_{23}H_{22}O_2S$		76.22	6.12	8.84
					76.82	6.06	9.04
2e	139	86	$C_{21}H_{18}O_2S$		75.43	5.43	9.60
					75.85	5.18	9.66
2f	163	91	$C_{23}H_{22}O_2S$		76.22	6.12	8.84
					76.50	6.04	9.10

The *Grignard* products **2a–2f**, listed in Table 1, are colourless, insoluble in cold aqueous 10% sodium hydroxide, give no colour with ethanolic ferric chloride, and are generally soluble in alcohol and benzene, but sparingly soluble in petroleum ether.

Action of Sulfuric Acid on 2,3-Dihydroxy-2,3-diaryl(aralkyl)-benzo[b]*thiophenes* (**2a–2f**). To a boiling solution of 0.50 g of each compound **2a–2f** in about 10 ml of glacial acetic acid, 2 drops of concentrated sulfuric acid were added. The mixture was refluxed for 15 min, then cooled and poured onto about 100 ml of water containing some crushed ice. The colourless product obtained was filtered off, washed with water and crystallized from ethyl alcohol.

The 3,3-diarylbenzo[*b*]thiophene-2-ones (**3a–3f**) listed in Table 2 are colourless, insoluble in cold aqueous sodium hydroxide, and generally soluble in ethanol and benzene but sparingly soluble in petroleum ether.

Table 2. *Pinacolones* (**3**) *from 2,3-Dihydroxy-2,3-diaryl(aralkyl)benzo*[b]*thiophenes* (**2**)

Pinacolone	m.p. °C	Yield %	Formula	Calc. Found	Analysis % C	H	S
3a	108	81	$C_{20}H_{14}OS$		79.45	4.63	10.59
					79.57	4.69	10.62
3b	126	78	$C_{22}H_{18}OS$		79.98	5.49	9.58
					80.00	5.80	10.10
3c	132	80	$C_{21}H_{16}OS$		79.73	5.10	10.12
					79.50	4.90	10.70
3d	155	80	$C_{23}H_{20}OS$		80.21	5.85	9.14
					80.48	5.60	9.20
3e	114	77	$C_{21}H_{16}OS$		79.73	5.10	10.12
					79.95	5.02	10.22
3f	118	82	$C_{23}H_{20}OS$		80.21	5.85	9.14
					80.62	5.60	9.36

Action of Benzene and Sulfuric Acid on 5-Methylbenzo[b]*thiophene-2,3-dione* (**1b**). To a cooled (0°) solution of 1.0 g of compound **1b** in about 50 ml of dry benzene, 4 ml of concentrated sulfuric acid was added dropwise so as to keep the temperature of the mixture below 5°. The mixture was kept at 0° for 5 days, then poured while stirring onto about 150 ml of water containing some crushed ice. After separation of the benzene layer, the aqueous layer was extracted with 30 ml of benzene. The combined benzene solution was evaporated under reduced pressure, and the residue was triturated with petroleum ether. The solid formed was crystallized from ethanol: colourless product, m.p. 132°, identified as the pinacolone rearrangement product **3c** by mixed melting point.

Action of Ethanolic Sodium Hydroxide on **3a** *and* **3c**. 1.0 g of each of **3a** and **3c** was refluxed in 20 ml of ethanolic sodium hydroxide (10%) for 2 h. After cooling, the solution was poured onto about 100 ml water with some crushed ice. The clear cold solution was acidified with concentrated hydrochloric acid, the colourless precipitate was filtered off, washed with cold water, and crystallized from ethanol: colourless crystals of **6a**, m.p. 203° and **6b**, m.p. 184°, both soluble in cold aqueous sodium carbonate with effervescence, and reprecipitated on acidification.

6a: $C_{20}H_{16}O_2S$ Calc. C 74.99 H 5.03 S 10.00% Found C 74.90 H 5.10 S 10.41%
6b: $C_{21}H_{18}O_2S$ Calc. C 75.43 H 5.43 S 9.60% Found C 75.71 H 5.26 S 9.90%

Cyclization of **6a** *by Acetic Anhydride*. To a solution of 0.50 g of acetic acid, 3 ml of acetic anhydride was added. The mixture was refluxed for 3 h, cooled and poured onto about 100 ml of water. After standing overnight, the precipitate formed was filtered, washed with water and crystallized from ethanol: colourless crystals, m.p. 108°, identified as **3a** by mixed melting point with the pinacolone rearrangement product of **2a**.

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214. Pyrimidine Derivatives and Related Compounds II: Synthesis of some Derivatives of Pyrimido[1,2:2′,3′]pyrazolo-[1,5-*a*]pyrimidines, a New Ring System

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Summary. 3,5-Diamino-4-phenylazo-pyrazoles (**1a–1c**) react with acetylacetone and with ethyl acetoacetate to yield the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **2a–2c** and **3a–3c**, respectively.

Whereas **1a–1c** add readily to methyl acrylate yielding the 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine derivatives **5a–5c**, **1a–1c** add to methylacrylonitrile or methyl methacrylate only under drastic conditions to yield **5d–5f**. The pyrimido[1,2:2′,3′]pyrazolo[1,5-*a*]pyrimidine derivatives **10a–10c** are prepared by the action of acrylonitrile on **2a–2c**. Compounds **10a–10c** are readily converted into the corresponding oxo derivatives **12a–12c** on treatment with acetic acid-hydrochloric acid mixture.

Earlier work in this laboratory directed for the synthesis of fused pyrimidines with bridgehead nitrogen [1] [2] stimulated an investigation of a possible route for the synthesis of substituted pyrimido[1,2:2′,3′]pyrazolo[1,5-*a*]pyrimidines, derivatives of a novel ring system. *Ried et al.* [3] have reported that 3-unsubstituted-2-amino-pyrazolo[1, 5-*a*]pyrimidines react with β-bifunctional reagents to yield pyrido[3, 4:3′, 4′]-pyrazolo[1, 5-*a*]pyrimidines. It seemed to us that 3-substituted-2-aminopyrazolo-[1,5-*a*]pyrimidines may react with bifunctional reagents to yield derivatives of the required ring system. Literature survey indicated that 3-substituted-2-amino-pyrazolo[1,5-*a*]pyrimidines have been prepared *via* a multistage inefficient synthesis [4] and only through pyrazolo[1,5-*a*]pyrimidine intermediates. In the present paper we report a convenient synthesis of a variety of 3-arylazo-2-aminopyrazolo[1,5-*a*]-pyrimidine derivatives from the readily obtainable 3,5-diamino-4-arylazopyrazoles **1a–1c** and on the utility of these pyrazolo[1,5-*a*]pyrimidines for the synthesis of a variety of arylazopyrimido[1,2:2′,3′]pyrazolo[1,5-*a*]pyrimidine derivatives. In this manner, the 2-amino-3-arylazo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine derivatives **2a–2c** were prepared by the action of acetylacetone on **1a–1c** in refluxing acetic acid. The structure of the products was supported by analytical and IR. data.

When the compounds **1a–1c** were treated with ethyl acetoacetate in refluxing acetic acid, the pyrazolo[1,5-*a*]pyrimidine derivatives **3a–3c** or possible isomeric **4a–4c** were obtained in high yields. Structure **3** was preferred on the basis of IR.