Summary

1. Four new 1-(β-dimethylaminoethyl)-benzimidazole derivatives containing various groups in the 2-position and 1-(β-dimethylaminoethyl)-benzotriazole hydrochloride have been prepared.
2. The results of preliminary pharmacological tests on these compounds for anti-histaminic activity is reported.
3. *o*-(β-Dimethylaminoethylamino)-nitrobenzene and *o*-(β-dimethylaminoethylamino)-aniline have been prepared.

KALAMAZOO, MICHIGAN RECEIVED JANUARY 7, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. IV.[1] Condensation of Biacetyl with Phenols

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While aromatic α-diketones, *e. g.*, benzil[2] and acenaphthenequinone,[3] are known to condense with phenol yielding tertiary aromatic monoketones of a pinacolone type, we have observed that the same is true also in the reaction of an aliphatic α-diketone, biacetyl. When biacetyl was condensed with phenol in the presence of sulfuric acid 2,2-bis-(*p*-hydroxyphenyl)-3-butanone (Ia)[4] was obtained. This butanone derivative was characterized by methylation which afforded 2,2-di-*p*-anisyl-3-butanone.[5,6]

The condensation of *o*-cresol and biacetyl gave an analogous product, 2,2-bis-(*p*-hydroxy-*m*-tolyl)-3-butanone (Ib). The structure of this new compound was assigned on the basis of analytical data as well as of its behavior as mentioned below.

Reduction of this condensation product (Ib) led to the corresponding alcohol (IIb), which was dehydrated under retro-pinacolone rearrangement to α,α′,3,3′-tetramethyl-4,4′-stilbenediol (IIIb). For confirmation of the structure the same stilbenediol was prepared by our previous method[6] starting from *p*-methoxy-*m*-methylacetophenone. The products of both procedures showed no depression in a mixed melting point determination.

Biological assay of this stilbene derivative (IIIb), which represents an isomer of diethylstilbestrol, has been carried out in the Laboratory of Prof. R. Kinosita of Osaka University Medical School. The new estrogen proved to be about one-half as active as diethylstilbestrol.

In contrast with these condensations, when *m*- or *p*-cresol was condensed with biacetyl, the reaction took a different course yielding a cyclic ether of a coumarano-coumarane type. Crystalline substances melting at 115° and 196–197°, respectively, were isolated from the products of the latter reactions. They are insoluble in caustic alkalies and accordingly are assumed to have no free phenolic hydroxyl groups.

Baker and McGowan[7] have prepared α-2,3,5,5′-tetramethylcoumarano-3′,2′,2,3-coumarane (IVa), m. p. 151°, by dehydrating the α-pinacol of *o*-acetyl-*p*-cresol (Va) with boiling acetic acid. Although they were unable to dehydrate the corresponding β-pinacol under the same condition, they did obtain a mixture of m. p. 150–183° by treatment with alcohol containing a trace of concentrated hydrochloric acid.

We have found that both the α- and β-pinacols afford a substance, m. p. 196–197°, upon treatment with a mixture of acetic acid and a trace of sulfuric acid.[8] In view of its alkali-insoluble character together with the analytical figures the product is considered to be the β-isomer of 2,3,5,5′-tetramethylcoumarano-3′,2′,2,3-coumarane (IVa) which the English authors failed to obtain in a pure state. This β-coumarano-coumarane derivative showed no depression of the melting point on admixture with the condensation product obtained from *p*-cresol and biacetyl.

Similar dehydration of the pinacols from 6-acetyl-*m*-cresol (Vb) led to 2,3,6,6′-tetramethylcoumarano-3′,2′,2,3-coumarane (IVb) and, indeed, depending on the dehydrating conditions mentioned above, either the α-compound, m. p. 139–140°, or the β-isomer, m. p. 115°, were obtained. The latter was found to be identical with the condensation product between biacetyl and *m*-cresol.

6,6′-Dihydroxy-2,3-dimethylcoumarano-3′,2′,-2,3-coumarane has been reported by Niederl and Nagel[9] in the condensation of biacetyl with resorcinol. The present condensation of *m*- or *p*-cresol with biacetyl seems to take a similar course. These cresols react ortho to the phenolic hydroxyl with biacetyl,[10] while phenol and *o*-cresol react at

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[1] Previous paper: Sisido and Nozaki, This Journal, **70**, 3326 (1948).

[2] Niederl, Niederl and Nagel, *ibid.*, **63**, 1235 (1941).

[3] Matei, *Ber.*, **62**, 2095 (1929).

[4] Adler, v. Euler and Gie, *Arkiv Kemi, Mineral. Geol.*, **18A**, No. 1, 21 pp. (1944). We thank the authors for the reprint.

[5] Price and Mueller, This Journal, **66**, 634 (1944).

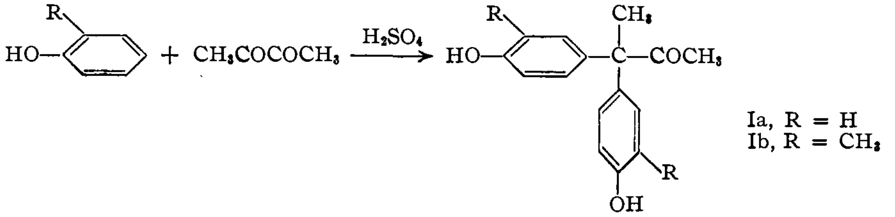
[6] Sisido and Nozaki, *ibid.*, **70**, 776 (1948).

[7] Baker and McGowan, *J. Chem. Soc.*, 559 (1937).

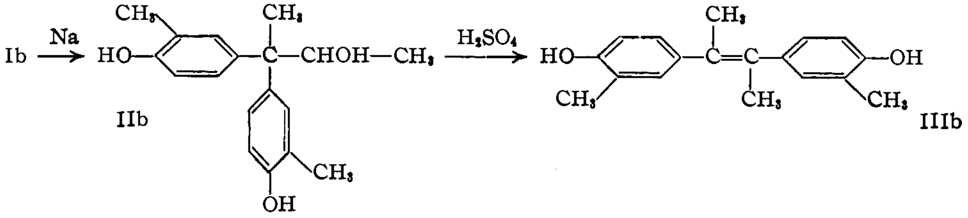
[8] *Cf.* Gie, *Arkiv Kemi, Mineral. Geol.*, **19A**, No. 11, 15 pp. (1945); *C. A.*, **41**, 1661 (1947).

[9] Niederl and Nagel, This Journal, **63**, 580 (1941).

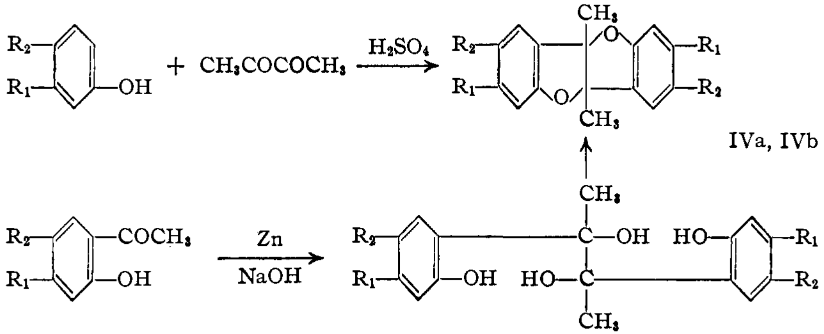
[10] The condensation of *m*-alkylphenols with ketones occurs usually ortho to the hydroxyl group. See for example: (a) Niederl, *ibid.*, **50**, 2230 (1928); (b) Niederl and Nagel, *ibid.*, **62**, 324 (1940); (c) Niederl and Ziering, *ibid.*, **62**, 1157 (1940); (d) Baker and Besly, *J. Chem. Soc.*, 1103 (1940).



Ia, R = H
Ib, R = CH_3



IIb
IIIb



IVa, IVb
Va, Vb
VIa, VIb

IVa, Va, VIa, R_1 = H, R_2 = CH_3
IVb, Vb, VIb, R_1 = CH_3, R_2 = H

the para position. If the explanation of Niederl, Niederl and Nagel[2] may be extended to these cases, the intermediate products formed at the initial stage of the condensations are assumed to be phenolhydrins of a pinacol type. In the pinacols which have phenolic hydroxyl groups at the respective ortho position (VIa, b) the dehydration occurs between aliphatic and aromatic hydroxyls to yield the cyclic ethers.[11] But the dehydration of the phenolhydrins with para nucleus hydroxyls occurs between side-chain hydroxyl under the pinacol–pinacolone rearrangement and results in the formation of ketones of a pinacolone type. We have, however, no positive evidence to decide whether these ketones are formed directly from the initial diketone or by the rearrangement from the phenolhydrins mentioned above.

In connection with these condensation reactions it is of interest that Ruggli, Herzog, Wegmann and Dahn[12] as well as Wegmann and Dahn[13] prepared arylacetoins by utilizing the condensation of biacetyl and its derivatives with aromatic hydrocarbons in the presence of aluminum chloride.

Although it was not possible to obtain from *m*-cresol an active isomer of diethylstilbestrol, *i. e.*, α,α',2,2'-tetramethyl-4,4'-stilbenediol[14] by the condensation with biacetyl, this latter estrogenic substance could, however, be prepared from *p*-methoxy-*o*-methylacetophenone through its pinacol and pinacolone compounds.[6] The melting points of the resulting 4,4'-stilbenediol and its dimethyl ether were found in accord with those reported by Hudson and Walton.[14]

In addition 2,3-bis-(*p*-methoxy-*o*-tolyl)-1,3-butadiene has been prepared by dehydrating the pinacol of *p*-methoxy-*o*-methylacetophenone with acetyl bromide.[15] Demethylation of the butadiene compound, however, failed to yield the free hydroxyl compound, because of its tendency to form a resinous product. Reduction of the 2,3-bis-(*p*-methoxy-*o*-toyl)-butadiene with metallic sodium resulted in the formation of 2,3-bis-(*p*-methoxy-*o*-tolyl)-2-butene[14]; the corresponding bibenzyl derivative[16,17] was not obtained in con-

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(11) It is true that there is no positive evidence for the coumarano-coumarane nucleus of all of the cyclic ethers mentioned above. The possibility of these compounds having a xanthene structure (and, therefore, a carbonyl group), such as those assigned by Matei[3] and by Matei and Bogdan (*Ber.*, **67**, 1834 (1934)) to the condensation products between acenaphthenequinone and resorcinol, hydroquinone, *p*-cresol, etc., however, was excluded, since the cyclic ethers (IVa, b) remained unchanged upon treatment with metallic sodium and alcohol. A 2',3',2,3-coumarano-coumarane with a ketone acetal structure also is not probable due to the stability of the compounds toward acidic (and basic) reagents.

In order to isolate such xanthene ketones, if present, from the mother liquors of the coumarano-coumaranes, we treated the filtrates with semicarbazide or with 2,4-dinitrophenylhydrazine, but were unable to obtain any crystalline derivatives. This fact, however, does not exclude the possibility of xanthenes being present in the neutral fractions, since Matei and others[3] have described that their xanthene ketones do not react with the so-called carbonyl reagents.

(12) Ruggli, Herzog, Wegmann and Dahn, *Helv. Chim. Acta*, **29**, 95 (1946); *C. A.*, **40**, 2819 (1946).

(13) Wegmann and Dahn, *ibid.*, **29**, 101 (1946); *C. A.*, **40**, 2820 (1946).

(14) Hudson and Walton, *J. Chem. Soc.*, 85 (1946); *C. A.*, **40**, 3425 (1946).

(15) Allen, Eliot and Bell, *Can. J. Research*, **17B**, 75 (1939); *C. A.*, **33**, 6284 (1939).

(16) Bretschneider, Bretschneider and Ajtai, *Ber.*, **74**, 571 (1941).

(17) Sisido and Nozaki, THIS JOURNAL, **70**, 778 (1948).

trast to 2,3-di-*p*-anisylbutadiene which yielded 2,3-di-*p*-anisylbutane.

Experimental[18]

I. Condensation of Biacetyl with Phenols

2,2-bis-(*p*-Hydroxyphenyl)-3-butanone (Ia).—To a solution of 7.0 g. of biacetyl and 17 g. of phenol in 35 cc. of glacial acetic acid, 20 cc. of 70% sulfuric acid was added with stirring and cooling in an ice-bath. After the addition was completed, which required about fifteen minutes, the cooling bath was removed and the temperature was raised gradually. After one and a half hours the reaction temperature reached 85° and was maintained at that point for an additional one hour. The contents were poured onto crushed ice and subjected to steam distillation. The residue was extracted several times with hot water, filtered and the filtrates were combined and allowed to cool. Crystals which separated from this aqueous solution were collected and recrystallized from dilute methanol. After drying over phosphorus pentoxide *in vacuo* colorless plates melting at 131–132° were obtained; yield, about 5 g. Adler, v. Euler and Gie[4] reported the m. p. 130°.

When the same reaction was repeated at low temperature with 98% sulfuric acid and without glacial acetic acid as in the case of *m*- or *p*-cresols described below, almost the same result was obtained.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.11; H, 6.22.

2,2-Di-*p*-anisyl-3-butanone.—The diphenol (Ia) was methylated with dimethyl sulfate and sodium hydroxide in the usual way and was recrystallized from a mixture of benzene and petroleum ether as colorless plates, m. p. 70–71°, which did not depress the m. p. when admixed with the authentic sample prepared from methoxyacetophenone.[6]

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.87; H, 6.90.

2,2-bis-(*p*-Hydroxy-*m*-tolyl)-3-butanone*[19] **(Ib).**—To a solution of 8.6 g. of biacetyl and 21.6 g. of *o*-cresol in 45 g. of glacial acetic acid was added 20 g. of 98% sulfuric acid and the mixture was treated in the same manner as above. The residue of the steam distillation was taken up in ether and extracted with 10% sodium hydroxide solution. The alkaline layer was separated, acidified with sulfuric acid and extracted with ether. This ether solution was washed with water, dried and evaporated. The residue which crystallized was collected, washed with benzene and dried. Yield of crude crystals, m. p. 154–155°, amounted to 13 g. Recrystallizations from dilute acetic acid furnished a pure sample of m. p. 156–157°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76:03; H, 7.09. Found: C, 75.82; H, 7.02.

2,2-bis-(*p*-Acetoxy-*m*-tolyl)-3-butanone*.—Three grams of the crude crystals was acetylated with acetic anhydride and pyridine. Recrystallizations from alcohol resulted in colorless needles, m. p. 128–129°. The yield was 2.6 g.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 72.02; H, 6.44.

When 2.0 g. of the product was hydrolyzed with 20 cc. of 10% alcoholic potash 1.5 g. of pure dihydroxy compound of m. p. 156–157° was regenerated.

2,3,6,6'-Tetramethylcoumarano-3',2',2,3-coumarane* (IVb).—To a solution of 8.6 g. of biacetyl in 21.6 g. of *m*-cresol 20 g. of 98% sulfuric acid was added under stirring and cooling with an ice-salt mixture. The addition required one hour, during which time the reaction temperature rose spontaneously to 15°. After standing overnight the product, which formed a black semi-solid mass, was extracted with ethyl acetate. The extract was washed with water and shaken out with 5% sodium hydroxide solution. Attempted isolation of a crystalline substance from the phenolic condensation products, which were obtained in about 2 g. as a black resin by acidifying the alkaline extracts was unsuccessful. The neutral organic layer was washed with water, dried and evaporated. Distillation of the residual oil under reduced pressure yielded 8.4 g. of a yellowish sirup which came over at 220–250° under 4 mm. Upon treating the product with methanol there was obtained 2.5 g. of crystals m. p. 112–113°, which formed colorless plates, m. p. 115°, after recrystallizations from alcohol and finally from petroleum ether.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.92; H, 6.83.

2,3,5,5'-Tetramethylcoumarano-3',2',2,3-coumarane* (IVa).—A mixture of 8.6 g. of biacetyl and 21.6 g. of *p*-cresol was treated in the same way as above with 20 g. of 98% sulfuric acid. The phenolic product weighed 3 g. and formed a black resin, from which nothing could be identified. Upon working up the alkali-insoluble condensation products, which weighed about 20 g., 2.2 g. of crystals, m. p. 194–195°, were isolated. Recrystallizations from alcohol afforded a pure substance melting at 196–197°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.86; H, 6.77.

II. Coumarano-coumarane Derivatives from Pinacols

2,3-bis-(*o*-Hydroxy-*p*-tolyl)-2,3-butanediol* (VIb).—A mixture of 20 g. of 6-acetyl-*m*-cresol (Vb), 20 g. of sodium hydroxide, 100 g. of zinc powder and 500 cc. of water was refluxed under stirring for ten hours according to the procedure of Baker and McGowan.[7] After cooling the mixture was filtered and the filtrate was acidified with 20% acetic acid. Solids which separated were collected, washed with water and dried[20]; yield of the pinacol mixture, m. p. 170–178°, amounted to 18 g. Recrystallizations from alcohol gave 3 g. of difficultly soluble α-pinacol (VIb) melting at 234–235°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.18; H, 7.17.

Upon concentration of the mother liquor the β-pinacol (VIb) crystallized in long prisms, which, after crystallizations from alcohol and drying *in vacuo*, melted at 188–190°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.68; H, 7.23.

α-2,3,6,6'-Tetramethylcoumarano-3',2',2,3-coumarane* (IVb).—A mixture of 1 g. of the α-pinacol (VIb) and 15 cc. of glacial acetic acid was refluxed for thirty minutes.[7] The solution was poured into water, extracted with ether and this ether solution was concentrated after washing and drying. The residue was recrystallized several times from alcohol. Thus were obtained 0.7 g. of colorless plates melting at 139–140°. The product did not dissolve in hot caustic alkalies.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.92; H, 6.75.

β-2,3,6,6'-Tetramethylcoumarano-3',2',2,3-coumarane* (IVb).—A mixture of 1.5 g. of the α-pinacol (VIb), 12 cc. of glacial acetic acid and 6 drops of concentrated sulfuric acid was heated on a water-bath for one hour. The product, when treated as above, gave 1 g. of colorless plates melting at 115°. Mixed melting point determination with the substance obtained in the condensation of biacetyl with *m*-cresol showed no depression.

Similar treatment of 5 g. of the β-pinacol (VIb) with acetic acid and sulfuric acid gave 3 g. of crystals, whose m. p. and mixed m. p. with the β-coumarano-coumarane derivative was 115°. The substance is insoluble in caustic alkalies.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.94; H, 6.70.

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(18) Microanalyses by Miss Kenko Ogawa of our Laboratory.

(19) Asterisk (*) indicates a new compound.

(20) Similar treatment of *p*-hydroxyacetophenone failed to afford the corresponding pinacol, 2,3-bis-(*p*-hydroxyphenyl)-2,3-butanediol. *Cf.* ref. 6 and Adler, Gie and v. Euler, U. S. Patent 2,421,401, June 3, 1947 or Swedish Patent 115,816, Feb. 12, 1946; *C. A.*, **41**, 486 (1947).

β-2,3,5,5′-Tetramethylcoumarano-3′,2′,2,3-coumarane* (IVa).—*o*-Acetyl-*p*-cresol (Va) was subjected to pinacolic reduction according to the method of Baker and McGowan[7] and the products were dehydrated with acetic acid and sulfuric acid in the same manner as the 2,3,6,6′-tetramethyl isomer. From 1 g. of the α-pinacol (VIa) 0.7 g., and from 2 g. of the β-pinacol (VIa) 1.6 g. of the same, alkali-insoluble cyclic ether, m. p. 196–197°, was obtained.[21] The substance did not depress the m. p. on admixture with the compound isolated from the condensation product between biacetyl and *p*-cresol.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.89; H, 6.96.

III. Syntheses of Stilbenediols

2,2-bis-(*p*-Hydroxy-*m*-tolyl)-3-butanol* (IIb).—To a solution of 10 g. of 2,2-bis-(*p*-hydroxy-*m*-tolyl)-3-butanone (Ib) in 100 cc. of alcohol was added during fifteen minutes under reflux 20 g. of sodium cut into small pieces. The mixture was then boiled until the sodium disappeared. The reaction mixture was acidified with dilute acetic acid and subjected to steam distillation. The residual solids were filtered and washed with ether; yield 9 g., m. p. 192–193°. Recrystallizations from a mixture of benzene and alcohol gave the alcohol melting at 193–194°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.54; H, 7.82.

α,α′,3,3′-Tetramethyl-4,4′-stilbenediol* (IIIb).—A mixture of 2 g. of the pinacolone alcohol (IIb) and 10 g. of glacial acetic acid was treated with a drop of concentrated sulfuric acid and heated on a boiling water-bath for five minutes. The resulting clear solution was poured into water and the solid which separated was collected, washed with water, dried and recrystallized from a mixture of benzene and alcohol. The product formed colorless plates, m. p. 197–198°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.14; H, 7.66.

The acetate* was prepared by the usual method. The product melted at 129–130° after recrystallizations from alcohol.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.84; H, 6.75.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-2,3-butanediol.*—To a solution of 28 g. of *p*-methoxy-*o*-methylacetophenone in 200 cc. of anydrous alcohol and 140 cc. of benzene was added 8.4 g. of coarse aluminum powder and 1 g. of mercuric chloride. The resulting mixture was treated as described in our previous paper.[6] The yield of the pinacol mixture, m. p. 121–135°, amounted to 21 g. Repeated crystallizations from ethyl acetate yielded a sample, m. p. 147–148°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.43; H, 7.71.

2,3-bis-(*p*-Methoxy-*m*-tolyl)-2,3-butanediol.*—Pinacolic reduction of 28 g. of *p*-methoxy-*m*-methylacetophenone carried out in the same way as above gave 20 g. of the corresponding pinacol mixture, m. p. 117–124°. Recrystallizations from petroleum ether and finally from ethyl acetate yielded colorless plates, m. p. 128–130°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.48; H, 7.50.

2,2-bis-(*p*-Methoxy-*o*-tolyl)-3-butanone.*—A mixture of 17 g. of the crude 2,3-bis-(*p*-methoxy-*o*-tolyl)-2,3-butanediol, 60 cc. of concentrated sulfuric acid and 80 cc. of water was stirred for one and a half hours on a boiling water-bath. The reaction product was poured into iced-water and extracted with ether. The ethereal extract was washed, dried and distilled. A yellowish oil came over at 220–235° under 6 mm. and weighed 10.6 g.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.52; H, 7.84.

2,2-bis-(*p*-Methoxy-*m*-tolyl)-3-butanone.*—When 10 g. of crude 2,3-bis-(*p*-methoxy-*m*-tolyl)-2,3-butanediol was treated with dilute sulfuric acid in the same way as above, 7.3 g. of a yellow viscous oil, b. p. 215–220° at 5 mm., was obtained.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.97; H, 8.00.

2,2-bis-(*p*-Methoxy-*o*-tolyl)-3-butanol.*—To a mixture of 10 g. of metallic sodium and 50 cc. of xylene heated at 140–170°, a solution of 8 g. of 2,2-bis-(*p*-methoxy-*o*-tolyl)-3-butanone in 40 cc. of anhydrous alcohol was added dropwise with stirring. After the addition was completed 60 cc. of alcohol was added in small portions. When metallic sodium had been consumed completely, the reaction product was poured into crushed ice and extracted with xylene. The xylene solutions were combined, washed with water and subjected to steam distillation in order to remove the solvent. Solids which separated from the residue were collected, dried and washed with a small quantity of ether. Thus were obtained 7.4 g. of white crystals melting at 107–109°. Recrystallization from alcohol gave a substance, m. p. 111°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.55; H, 7.87.

2,2-bis-(*p*-Methoxy-*m*-tolyl)-3-butanol.*—When 7.0 g. of 2,2-bis-(*p*-methoxy-*m*-tolyl)-3-butanone was reduced with 10 g. of metallic sodium, 50 cc. of xylene and 100 cc. of absolute alcohol, there was obtained an oily carbinol, which was subjected immediately to the retro-pinacolone rearrangement as described below.

α,α′,2,2′-Tetramethyl-4,4′-stilbenediol.—Several drops of dilute sulfuric acid were added to 7 g. of 2,2-bis-(*p*-methoxy-*o*-tolyl)-3-butanol and the mixture was distilled under reduced pressure. The distillate, b. p. 195–205° at 5 mm., solidified, yield, 6.0 g. Recrystallizations from alcohol gave 2,3-bis-(*p*-methoxy-*o*-tolyl)-2-butene in colorless plates, m. p. 100–101°. Hudson and Walton[14] reported the m. p. 97–98°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.01. Found: C, 81.36; H, 7.74.

Oxidation of this butene derivative with chromic anhydride in acetic acid yielded *p*-methoxy-*o*-methylbenzoic acid, m. p. 175–176°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.14; H, 5.85.

Demethylation of 4 g. of the butene derivative with a Grignard reagent[6] followed by recrystallizations from benzene and finally from 70% alcohol gave 2 g. of the stilbenediol in colorless plates, m. p. 214°. Hudson and Walton[14] described the m. p. 208–210°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.93; H, 7.60.

The acetate* prepared by treating this stilbenediol with a mixture of acetic anhydride and pyridine formed colorless plates melting at 116–117°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.83; H. 6.97.

α,α′,3,3′-Tetramethyl-4,4′-stilbenediol* (IIIb).—The reduction product of 7 g. of 2,2-bis-(*p*-methoxy-*m*-tolyl)-3-butanone obtained above was distilled under reduced pressure in the presence of a trace of sulfuric acid. There was obtained 4.8 g. of a colorless distillate, b. p. 195–205° at 5 mm., which solidified immediately. Recrystallizations from alcohol and finally from a mixture of benzene and petroleum ether yielded **2,3-bis-(*p*-methoxy-*m*-tolyl)-2-butene*** in colorless plates, m. p. 120–121°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.01. Found: C, 80.72; H, 8.38.

Upon oxidation of this stilbene compound with chromic anhydride in acetic acid *p*-methoxy-*m*-methylbenzoic acid was obtained in colorless prisms, m. p. 194–195°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.87; H, 6.02.

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(21) Gie (ref. 8) described a rearrangement of β-coumarano-coumaranes into the corresponding α-isomers by the action of a mixture of acetic acid and concentrated hydrochloric acid. Attempted isomerization of our β-coumarano-coumarane into the α-isomer of Baker and McGowan (ref. 7), however, failed.

Demethylation of 2 g. of this butene derivative followed by recrystallizations from benzene–alcohol as above yielded 1.5 g. of phenolic substance in colorless plates, m. p. 197–198°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.64; H, 7.76.

The **acetate*** formed colorless plates, m. p. 129–130°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.86; H, 6.72.

This stilbenediol and the acetate showed no depression of the melting points on admixture with the specimens prepared from the condensation product between biacetyl and *o*-cresol.

2,3-di-*p*-Anisyl-1,3-butadiene.*—To a mixture of 8 g. of 2,3-di-*p*-anisyl-2,3-butanediol[6] and 0.5 g. of phenyl-β-naphthylamine, 23 cc. of acetyl bromide[15] was added dropwise with stirring and cooling with an ice-bath. After the excess of acetyl bromide was distilled off under reduced pressure, the residue was poured into 10% sodium carbonate solution and extracted with benzene. The benzene solution was washed with water, dried and distilled. There was obtained 5 g. of a fraction, b. p. 225–235° under 11 mm., which was dissolved in a hot mixture of benzene and methanol and allowed to cool. Recrystallizations of the solids thus obtained from the same solvent yielded 2.5 g. of colorless prisms, m. p. 108–109°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.84; H, 6.99.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-1,3-butadiene.*—Ten grams of 2,3-bis-(*p*-methoxy-*o*-tolyl)-2,3-butanediol was dehydrated with 25 cc. of acetyl bromide in the same manner as above, yielding 4 g. of a fraction, b. p. 200–210° at 5 mm., from which 2.6 g. of colorless prisms melting at 108–108.5° were obtained after recrystallizations from a mixture of alcohol and benzene.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.67; H, 7.28.

2,3-Di-*p*-anisylbutane.—Reduction of 2.5 g. of the di-*p*-anisylbutadiene with 4.5 g. of metallic sodium, 60 cc. of anhydrous alcohol and 25 cc. of xylene was carried out in the same way as in the preparation of 2,2-bis-(*p*-methoxy-*o*-tolyl)-3-butanol. Recrystallizations of the product from ligroin gave 1 g. of colorless prisms, m. p. and mixed m. p. with the *meso*-form of 2,3-di-*p*-anisylbutane[17] 133–133.5°.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-2-butene.—To a solution of 1.2 g. of the above ditolylbutadiene derivative in 24 cc. of absolute alcohol was added, under refluxing, 2.5 g. of metallic sodium in small portions. The product was treated in the usual way and recrystallized from alcohol. There were obtained 0.7 g. of colorless prisms, m. p. and mixed m. p. with the above-mentioned 2,3-bis-(*p*-methoxy-*o*-tolyl)-2-butene 100–101°.

Summary

Condensation of biacetyl with phenol or with *o*-cresol resulted in the formation of a diphenolic ketone, 2,2-bis-(*p*-hydroxyphenyl)-3-butanone or 2,2-bis-(*p*-hydroxy-*m*-tolyl)-3-butanone, respectively.

Condensation of biacetyl with *m*- or *p*-cresol took a different course, yielding 2,3,6,6'-tetramethyl- or 2,3,5,5'-tetramethylcoumarano-3',2',-2,3-coumarane, respectively.

These coumarano-coumaranes were synthesized by a different route, starting from 6-acetyl-*m*-cresol and from *o*-acetyl-*p*-cresol, respectively.

Two isomers of diethylstilbestrol, *i. e.*, α,α',2,2'-tetramethyl-4,4'-stilbenediol and α,α',3,3'-tetramethyl-4,4'-stilbenediol were prepared.

KYÔTO, JAPAN RECEIVED OCTOBER 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

A Novel Rearrangement of a Piperidine Ring

BY ROBERT H. REITSEMA[1]

A ring contraction in the piperidine series has been observed during a study of the methods of synthesis of 3-aminopiperidines.[2] 3-Chloropiperidines are readily available as a result of Paul's synthesis of 3-hydroxypiperidines from tetrahydrofurfuralamines.[3] Treatment of 1-ethyl-3-chloropiperidine with benzylamine did not give the expected 3-benzylaminopiperidine, however. Instead, a compound which is apparently 1-ethyl-2-benzylaminomethylpyrrolidine was obtained. A similar anomalous result was found when the product from the reaction of 1-methyl-3-chloropiperidine and benzylamine was compared with authentic 1-methyl-3-benzylaminopiperidine.

The nature of the product of the reaction was elucidated by various techniques. The material was recovered unchanged after it had been boiled six hours in concentrated hydrochloric acid. Its titration curve was very similar to that of a 4-benzylaminopiperidine. These observations eliminated the possibility that a 2-benzylaminopiperidine had formed by attack of the benzyl group at the 2-position after removal of the chlorine ion or after dehydrohalogenation. A 2-aminopiperidine is an aminoacetal and would not be stable to acids or have a normal titration curve. Mixed melting points of the picrates with the corresponding 4-benzylaminopiperidine picrates showed that a rearrangement to the 4-position had not taken place. A monomeric structure for the compound was shown by a molecular weight determination and by consideration of boiling points. Only one active hydrogen could be detected and no absorption of hydrogen occurred either in the presence of platinum oxide at room temperature and atmospheric pressure or in the presence of Raney nickel at elevated temperature and pressure. Thus a linear structure was not possible since that would require a double bond and two active hydrogens.

The only likely explanation of the reaction is that the new compounds are 2-aminomethylpyrrolidine derivatives. It has been well established

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[1] Present address: A. M. Todd Co., Kalamazoo, Mich.

[2] Reitsema and Hunter, THIS JOURNAL, **71**, 1680 (1949).

[3] Paul, *Compt. rend.*, **221**, No. 15, 412 (1945).