50 ml. of benzene and combined with the xylene–ligroin filtrate. The combined organic solution was extracted with three 60-ml. portions of 5% potassium hydroxide, then evaporated to dryness. The residue was crystallized twice from a 1:3 benzene–ethanol mixture to give 1.24 g. (38.7%) of pale yellow material melting at 170–172°. Sublimation of this material at 160° (0.01 mm.) and recrystallization of the sublimate from the same solvent mixture afforded white needles melting at 172–173°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 93.57; H, 6.39.

4-(Methyl-1-cyclohexen-1-yl)-*p*-terphenyl.—Using the same quantities and conditions as described for the 2-methyl isomer, there was obtained 6.25 g. (49%) of shiny plates from benzene which melted at 200° with decomposition.

Anal. Calcd. for $C_{25}H_{24}$: C, 92.59; H, 7.41. Found: C, 92.31; H, 7.72.

3-Methyl-*p*-quaterphenyl.—Chloranil oxidation as above and recrystallization from benzene afforded a 62% yield of nearly white plates melting at 244–245.5°. The analytical sample was obtained by sublimation at 210° (0.01 mm.) and melted at 245–246°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 93.43; H, 6.51.

4-(4-Methyl-1-cyclohexen-1-yl)-*p*-terphenyl.—Once again the same quantities and conditions were employed; however, the crude product after treatment with Lucas reagent melted over the range 205–235° and resisted purification by recrystallization. The crude material was sublimed at 200° (0.01 mm.) to provide 3.15 g. (32%) of white material with a melting range of 204–208°. Recrystallization from benzene raised this to 208° with decomposition.

Anal. Calcd. for $C_{25}H_{24}$: C, 92.59; H, 7.41. Found: C, 92.69; H, 7.42.

4-Methyl-*p*-quaterphenyl.—4-(4-Methyl-1-cyclohexen-1-yl)-*p*-terphenyl (1.62 g., 0.005 mole) was dehydrogenated with 2.48 g. (0.010 mole) of chloranil in 25 ml. of xylene by refluxing for 8 hr. Upon dilution of the xylene solution with petroleum ether as before, both the product and the dihydrochloranil precipitated. This mixture was extracted continuously with hot ethanol to remove dihydrochloranil and then with toluene which dissolved the desired product. When cooled, the toluene extract deposited 1.05 g. (65.6%) of nearly white plates having a melting range of 322–329°. Sublimation at 210° (0.01 mm.), followed by recrystallization from toluene, afforded 0.64 g. (38%) of clear plates melting at 328–330°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 94.04; H, 5.98.

4,4′-Bis-(methyl-1-cyclohexen-1-yl)-biphenyl.—To a solution of 0.025 mole of 4,4′-biphenylenedilithium[9] in 100 ml. of 1:1 benzene–ether was added, over a period of 30 minutes, a solution of 5.72 g. (0.051 mole) of 2-methylcyclohexanone in 50 ml. of benzene. The resulting gray-green suspension was stirred at gentle reflux for 3 hr., then hydrolyzed with 50 ml. of 10% hydrochloric acid. The layers were separated and the organic layer washed with water and filtered from a trace of solid material. This solution was distilled until the temperature had reached 60° and the remaining benzene solution stirred at gentle reflux with 60 ml. of Lucas reagent for 2 hr. The oily solid obtained from the organic layer was crystallized from 100 ml. of ethanol to give 1.51 g. (18%) of shiny plates having a melting range of 98–103°. Two recrystallizations from ethanol raised the melting point to 107–108°. The analytical sample melted at 108.5–109°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 91.07; H, 8.86.

2,2‴-Dimethyl-*p*-quaterphenyl.—The octahydro derivative (1.37 g., 0.004 mole) was treated with 3.94 g. (0.016 mole) of chloranil in 25 ml. of refluxing xylene for 12 hr. to give 0.59 g. (44%) of crude product melting over the range 125–134°. Sublimation at 120° (0.01 mm.) gave white needles having a melting range of 142–146°. Four recrystallizations from ethanol produced a pure sample melting at 150–151°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.41; H, 6.59. Found: C, 93.45; H, 6.58.

4,4′-Bis-(methyl-1-cyclohexen-1-yl)-biphenyl.—Employing quantities and conditions identical to those used for the 2-methyl isomer there was obtained 3.32 g. (39%) of pale yellow material melting at 144–146°. After four recrystallizations from 1:1 ethanol–benzene the shiny, white plates melted at 149–150°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 91.31; H, 8.77.

3,3‴-Dimethyl-*p*-quaterphenyl.—Chloranil oxidation of 1.67 g. (0.005 mole) of 4,4′-bis-(methyl-1-cyclohexen-1-yl)-biphenyl produced 0.41 g. (24%) of nearly white material having a melting range of 210–215°. Sublimation at 210° (0.01 mm.) left 0.30 g. (19%) of clear plates melting at 214–215°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.41; H, 6.59. Found: C, 93.24; H, 6.64.

4,4′-Bis-(4-methyl-1-cyclohexen-1-yl)-biphenyl.—Again using the same quantities and conditions as in the preparation of the 2-methylcyclohexenyl derivative, there was recovered 2.70 g. (31%) of shiny white plates which gradually melted to a yellow-orange liquid over the range of 215–223°. Two recrystallizations from benzene left 2.20 g. (26%) which decomposed at 225°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 90.77; H, 8.91.

4,4‴-Dimethyl-*p*-quaterphenyl.—Oxidation of 1.67 g. (0.005 mole) of the bis-cyclohexene compound prepared above with chloranil gave 0.81 g. (58%) of gray powder which charred slowly above 320°. After sublimation at 210° (0.01 mm.) and recrystallization from toluene there was recovered 0.26 g. (18%) of white powder melting at 338–340°. Pummerer and Seligsberger[10] reported 334° for this compound.

(9) H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2327 (1940).

(10) J. Pummerer and F. Seligsberger, *Ber.*, **64B**, 2485 (1931).

AMES, IOWA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, VETERANS ADMINISTRATION HOSPITAL]

Studies in the Naphthalene Series. III. Synthesis of Apogossypol Hexamethyl Ether[1]

BY J. D. EDWARDS, JR., AND J. L. CASHAW

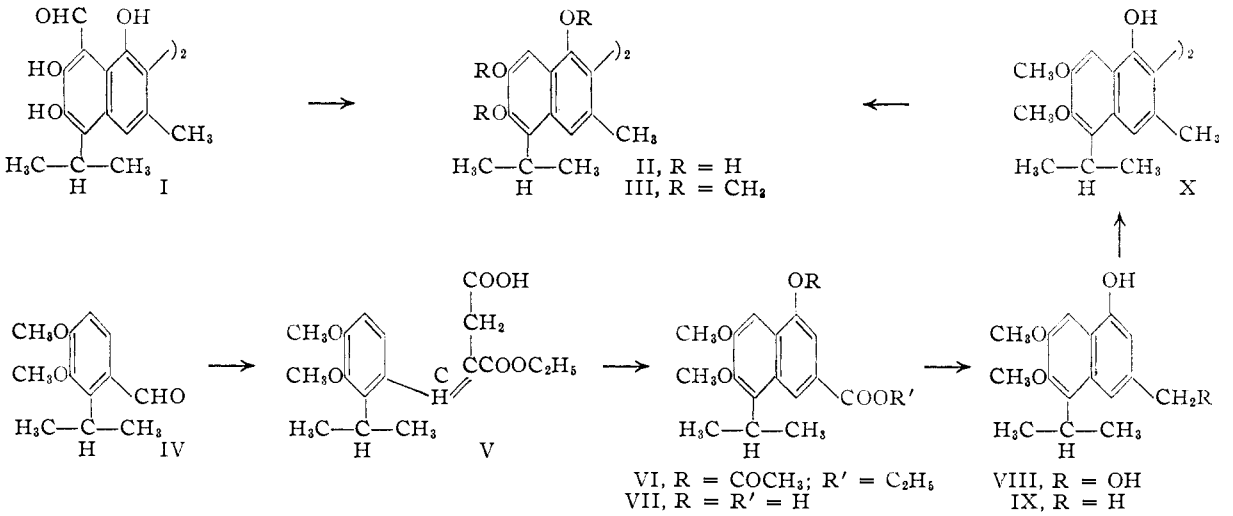
RECEIVED NOVEMBER 16, 1956

Apogossypol hexamethyl ether, the primary degradation product of gossypol, the pigment and toxic principle in cottonseed, formulated by Adams as 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl has been synthesized by the oxidative coupling of 5-isopropyl-1,6,7-trimethoxy-3-methyl-1-naphthol and methylation of the resulting binaphthol.

Gossypol, the yellow pigment of cottonseed, has been the subject of extensive work[2] and was for-

(1) Preliminary communication: J. D. Edwards, Jr., and J. L. Cashaw, THIS JOURNAL, **78**, 3224 (1956).

(2) For a review of these studies see F. Mayer and A. H. Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 114–117; R. D. Haworth, *Ann. Repts. Progr. Chem.* (Chem. Soc. London), **36**, 284 (1939); C. H. Boatner "Cottonseed and Cottonseed Products," edited by A. E. Bailey, Interscience Publishers, Inc., New York, N. Y., 1948, Chap. VI, pp. 213–363.



mulated by Adams[3] as 2,2'-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-formylnaphthyl (I), as a result of his degradation studies. The postulated structure of desapogossypolone tetramethyl ether[3] was later shown to be correct by synthesis.[4] Heating of gossypol in concentrated sodium hydroxide results in the formation of apogossypol[5-7] (II), which is very unstable even in the solid state. Methylation gives apogossypol hexamethyl ether (III) which was, to a large extent, used for the degradation studies by Adams.[3]

The synthesis reported in this communication establishes conclusively the correctness of Adams' formulation[3] as to the relationship of the internuclear linkage and the groups at the 1-, 3- and 5-positions in apogossypol and desapogossypol hexamethyl ethers. This relationship has been questioned recently.[8]

The synthesis of 5-isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (IX), the key intermediate in the synthesis here reported, utilized 2-isopropyl-3,4-dimethoxybenzaldehyde (IV)[9] as the starting material. The condensation of IV with diethyl succinate gave the half-ester V. Cyclodehydration of V with sodium acetate and acetic anhydride[10] gave the acetate VI which on saponification yielded 1-hydroxy-5-isopropyl-6,7-dimethoxy-3-naphthoic acid (VII). Reduction of VII with lithium aluminum hydride gave 3-hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (VIII). Hydrogenolysis of VIII with palladium-on-charcoal gave the naphthol IX.

In the preliminary studies[1] the oxidative coupling of IX to 2,2'-bi-1-(5-isopropyl-6,7-dimethoxy-3-methyl)-naphthol (X)[11] was achieved in a low yield by use of ferric chloride[12] with purified dioxane as the solvent. Later it was found that the coupling of IX to X occurred in quantitative yield by merely heating IX above its melting point. The over-all yield from IV to X was 26%. Methylation of X using aqueous dioxane as the solvent gave 2,2'-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III) identical in all respects with apogossypol hexamethyl ether (III) prepared from gossypol.

Acknowledgment.—The encouragement and interest of Professor R. B. Turner is gratefully acknowledged.

Experimental[13]

1-Hydroxy-5-isopropyl-6,7-dimethoxy-3-naphthoic Acid. (a) **Stobbe Condensation.**—To a mixture of 3.8 g. of sodium hydride in 30 ml. of anhydrous benzene there was added with stirring a solution of 27 g. of diethyl succinate and 11 g. of 2-isopropyl-3,4-dimethoxybenzaldehyde[9] in 50 ml. of benzene. This mixture was heated at 50° for 1 hr. after 0.75 ml. of alcohol was added. After cooling, water was added and the mixture extracted with ether. The aqueous phase was acidified and extracted with ether. The two ethereal extracts were combined and extracted with 250 ml. of 5% sodium carbonate solution. The aqueous extract was cooled and acidified with dilute hydrochloric acid. The oily precipitate was taken up in ether and dried over anhydrous sodium sulfate. Evaporation of the ether gave 14.2 g. (80%) of the oily half-ester V.

(b) **Ring Closure and Saponification.**—To 14.2 g. of the crude half ester, there was added 63.5 ml. of acetic acid, 63.5 ml. of acetic anhydride and 3 g. of fused sodium acetate. After refluxing for 4 hr., the light yellow solution was evaporated under a current of air and the semi-crystalline residue treated with 100 ml. of 5% sodium carbonate. The product was extracted with ether, and after drying over sodium sulfate, the ether was removed over a steam-bath. The crude oily product VI was then treated with 350 ml. of methanol and 350 ml. of 10% sodium hydroxide and refluxed for 3 hr. The alcohol was evaporated over a steam-bath and the aqueous extract acidified to give 10.6 g. (86%) of

(3) R. Adams, R. C. Morris, T. A. Giessman, D. J. Butterbaugh and E. C. Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(4) R. Adams and B. R. Baker, *ibid.*, **63**, 535 (1941).

(5) F. E. Carruth, *ibid.*, **40**, 647 (1918).

(6) E. P. Clark, *J. Biol. Chem.*, **78**, 159 (1928).

(7) R. Adams and D. J. Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

(8) D. A. Shirley and W. L. Dean, *ibid.*, **77**, 6077 (1955).

(9) J. D. Edwards, Jr., and J. L. Cashaw, *ibid.*, **78**, 3821 (1956).

(10) W. S. Johnson and R. B. Graber, *ibid.*, **72**, 933 (1950).

(11) Since methylation of the binaphthol obtained gave a product identical with apogossypol hexamethyl ether, there can be no question that the coupling occurred at the 2-position in IX. This follows since desapogossypolone tetramethyl ether, which is obtained from apogossypol hexamethyl ether, has been shown[3] by synthesis to possess the 2,2'-linkage. A study of Fisher-Taylor-Hirschfelder models also shows that the 4-position in IX is so masked by the metbyl and isopropyl groups that no coupling to give the 4,4'-bi-1-naphthol can occur.

(12) J. D. Edwards, Jr., and J. L. Cashaw, THIS JOURNAL, **76**, 6141 (1954).

(13) All analyses were done by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. Melting points are uncorrected and were made on a Fisher-Johns apparatus. The infrared determinations were carried out on a Perkin-Elmer model 21 spectrophotometer, 0.11-mm. cells, solvent chloroform, concentration approximately 7%.

VII. Crystallization from benzene gave material of m.p. 226–227°. The infrared spectrum[13] exhibited carbonyl absorption at 1680 and hydroxyl absorption at 3380 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.18; H, 6.26. Found: C, 66.32; H, 6.23.

3-Hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (VIII).—To 4 g. of lithium aluminum hydride in 200 ml. of absolute ether there was added dropwise a solution of 4.5 g. of VII in 100 ml. of ether. The mixture was refluxed for 90 minutes and allowed to stand overnight. After cooling, the mixture was decomposed by the dropwise addition of water and then acidified with dilute hydrochloric acid. After separation, the ethereal extract was washed twice with water and dried over anhydrous sodium sulfate. The ether was removed over a steam-bath and the residue crystallized from benzene to give 3.9 g. (93%) of VIII, m.p. 207–209°. The infrared spectrum[13] showed hydroxyl group absorption at 3420 and 3300 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.53; H, 7.31. Found: C, 69.71; H, 7.20.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (IX).—To 0.15 g. of palladium-on-charcoal (10%) in 35 ml. of methanol there was added 0.5 g. of VIII in 65 ml. of methanol. One drop of concd. hydrochloric acid in 1 ml. of water was added to this mixture. It was then hydrogenated for 20 minutes in a Parr low pressure hydrogenator. Anhydrous sodium sulfate was added and the mixture suction filtered. After removal of the methanol over a steam-bath, the product was recrystallized from chloroform–petroleum ether (30–60°) to give 0.192 g. (41%) of IX, m.p. 129–130°. The infrared spectrum[13] showed the presence of an hydroxyl group (sharp band at 3570 and a broad band at 3310 cm.$^{-1}$).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.76; H, 7.78.

2,2′-Bi-1-(5-isopropyl-6,7-dimethoxy-3-methyl)-naphthol (X).—A test-tube containing 0.2 g. of IX was placed in an oil-bath heated to 150°; the temperature was allowed to rise to 215° and held there for 20 minutes or until the material had melted and solidified. The product was recrystallized from benzene–methanol to give a quantitative yield of X, m.p. 271–274°.

Anal. Calcd. for $C_{32}H_{38}O_6$: C, 74.10; H, 7.38; mol. wt., 518. Found: C, 74.21; H, 7.39; mol. wt. (Rast), 447.

2,2′-Bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III).—To a solution of 0.24 g. of X in 25 ml. of purified dioxane[14] there was added 5 ml. of an aqueous solution of 0.49 g. of potassium hydroxide. To this mixture there was added 1.1 g. of dimethyl sulfate which was then heated under reflux until reaction was complete as indicated by litmus paper. The additions of potassium hydroxide and dimethyl sulfate were repeated two times. After cooling, water was added and the reaction mixture extracted with dichloromethane. The dichloromethane phase was extracted several times with water. After drying over anhydrous sodium sulfate, the dichloromethane was removed over a steam-bath and the residue taken up in 25 ml. of diethyl ether and filtered. Upon standing 0.1 g. (42%) of 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III) crystallized. It was recrystallized several times from benzene–methanol, m.p. 277–279°; mixture m.p. with apogossypol hexamethyl ether prepared from gossypol, 277–278°. The infrared[13] spectra of the natural and synthetic product were indistinguishable.

(14) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 285.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

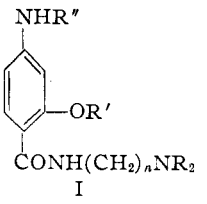
Derivatives of 4-Amino-2-hydroxybenzoic Acid. IV. Amides

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR, HELEN G. BATES AND PATRICIA M. CARROLL

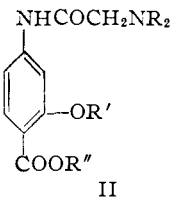
RECEIVED OCTOBER 15, 1956

Several types of amides derived from the 4-amino-2-hydroxybenzoic acid nucleus have been prepared. The first type consisted of N-(dialkylaminoalkyl)-4-amino-2-hydroxybenzamides and the related 2-alkoxy and 4-alkylamino compounds. Several of these compounds possessed outstanding activity as antifibrillatory agents. The second series was of the general type represented by an alkyl 4-(dialkylaminoacetylamino)-2-alkoxybenzoate and its related derivatives. The latter compounds were, in general, only fair local anesthetics but in certain cases possessed substantial analgesic properties. Finally, a series of variants on the 4-amino-2-alkoxybenzamide nucleus were prepared; certain of these compounds were potent oral analgesics.

The observation[1] that a very high degree of local anesthetic activity was associated with certain basic ester and thiol ester derivatives of 4-amino-2-hydroxy- and 2-alkoxybenzoic acids[2] prompted an extension of the synthetic work to two types of basic amides related to these series, as depicted in I and II.



I



II

Previously published investigations[3–5] of N-ω-dialkylaminoalkylbenzamides have shown that the simple amides were considerably less active as local anesthetics than their ester counterparts and that even in the cases of 3-alkoxy-[4] or 4-alkoxy-[5] substitution the local anesthetic activity does not surpass that of the esters. However, since in the present series a very high degree of local anesthetic activity was associated with the basic ester counterparts[1] of I, it was felt that a reduction in the degree of local anesthetic activity would not be a serious defect. Further, the increased stability of the amide linkage toward hydrolysis might well be reflected in more desirable physiological properties.

The synthesis of the amides of type II was based upon the premise that the low toxicity associated

(1) F. P. Luduena and J. O. Hoppe, *J. Pharmacol. Exptl. Therap.*, **104**, 40 (1952), and subsequent papers.

(2) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador and Mary Wilson, THIS JOURNAL, **73**, 3674 (1951); (b) **74**, 592 (1952); (c) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **76**, 5121 (1954).

(3) H. Wenker, *ibid.*, **60**, 1081 (1938); F. F. Blicke, H. C. Parke and E. L. Jenner, *ibid.*, **62**, 3316 (1940); R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3839 (1949).

(4) J. Büchi, E. Stünzi, M. Flury, R. Hirt, P. Labbart and L. Ragaz, *Helv. Chim. Acta*, **34**, 1002 (1951).

(5) P. Kolosy, P. Teyssie and H. Vanderhaeghe, *J. Pharm. Pharmacol.*, **7**, 477 (1955).