PART 1: CHEMISTRY

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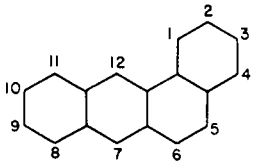
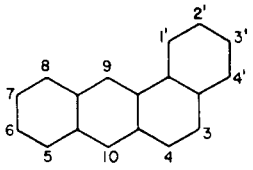
Nomenclature of BAs

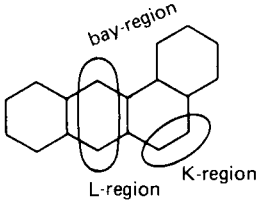
Some confusion exists in the literature because of different names and numbering systems that have been used. In this book BA refers to benz[a]anthracene whose numbering system is shown and compared to that of 1:2-benzanthracene which is no longer in use. Older titles have been given modern nomenclature. The naming of different areas in BA is illustrated on the formula: K- and L-regions (Pullman and Pullman, 1954), and bay region (Jerina and Daly, 1976). Positions 7 and 12 are often referred to as the *meso* positions.



Benz[a]anthracene (occasionally called tetraphene with the same numbering as for BA)



1:2-benzanthracene



Purification of BAs

Reaction of most of the polynuclear aromatic hydrocarbons with compounds such as picric acid, 1,3,5-trinitrobenzene, and 2,4,7-trinitrofluorenone results in the formation of molecular complexes. These complexes have proved to be extremely useful for purposes of characterization and purification since the hydrocarbon portion of the complex can be readily recovered either by chromatography or by treating a solution of the complex with a base (Brass and Fanta, 1936; Orchin and Woolfolk, 1946).

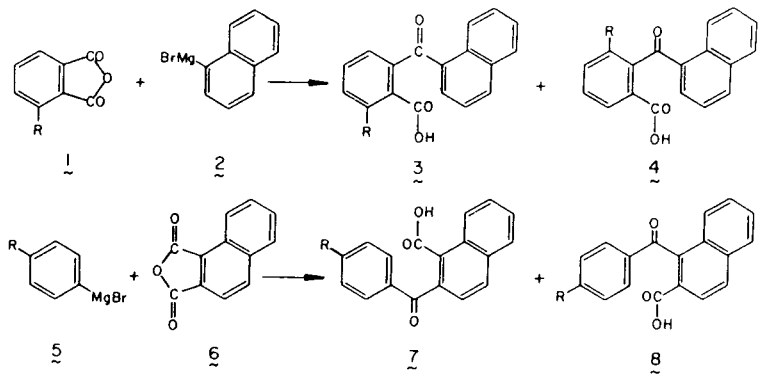
1

Synthetic routes from benzenes and naphthalenes

1.1 The ketoacid route

The two most widely used routes to BA compounds having methyl groups in the 7-, 12- or 7,12-positions and other groups such as F, Cl, Br, OCH_3 in various positions involve condensation of a naphthylmagnesium bromide, **2**, with a phthalic anhydride, **1**, or a phenylmagnesium bromide **5**, with a 1,2-naphthalic anhydride, **6** (see Scheme I). The former reaction affords a mixture of acids, **3** and **4**,

Scheme I. Condensation of Anhydrides with Grignard Reagents

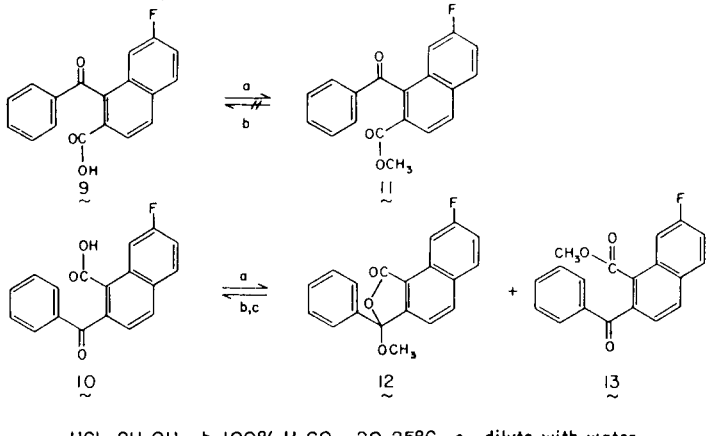


while the latter yields **7** and **8**. For convenience in further discussion, acids of types **3** and **7** will be called hindered acids while acids of types **4** and **8** will be called unhindered acids. Similar mixtures of ketoacids are obtained by Friedel–Crafts condensation of **1** and **6**, with naphthalenes and benzenes, respectively. In general the route involving Grignard reagents is preferable to that using Friedel–Crafts condensations. For

example, when 3-fluorophthalic anhydride is condensed with naphthalene not only does reaction occur at each carbonyl group of the anhydride but also at the 1- and 2-positions of naphthalene (Newman and Blum, 1964*d*; Sheikh *et al.*, 1979). Early studies on the reactions shown in Scheme I have been reviewed (Fieser, 1937).

In the early work leading to acids of types **3**, **4**, **7** and **8** separation into pure isomers was accomplished by fractional recrystallization. In later work, differences in chemical reactivity were used to simplify separation. For example, when the mixture of acids, **9** and **10**, formed by the Friedel–Crafts reaction of 7-fluoro-1,2-naphthalic anhydride with benzene, was esterified a mixture of normal esters, **11** and **13**, and pseudo ester, **12**, was obtained (see Scheme II). After keeping this ester mixture

Scheme II Separation of Ketoacid Mixtures



a. HCl, CH_3OH b. 100% H_2SO_4, 20–25°C c. dilute with water

in 100% sulphuric acid at 20–25°C for 3 h and then pouring on to ice, the products were separated into acid and neutral fractions. The acid fraction was almost pure **10**, while on alkaline hydrolysis of the neutral fraction almost pure **9** was obtained (Newman *et al.*, 1961). Other examples of this method of separation have been given by Newman and Scheurer (1956), Newman and Blum (1964*a*,*b*,*d*), Newman *et al.* (1972) and Newman *et al.* (1978*b*). The success of this method is based on earlier chemical and mechanistic studies on normal and pseudo esters of *o*-benzoylbenzoic acid types (Newman and McCleary, 1941*a*,*b*; Newman *et al.*, 1945).

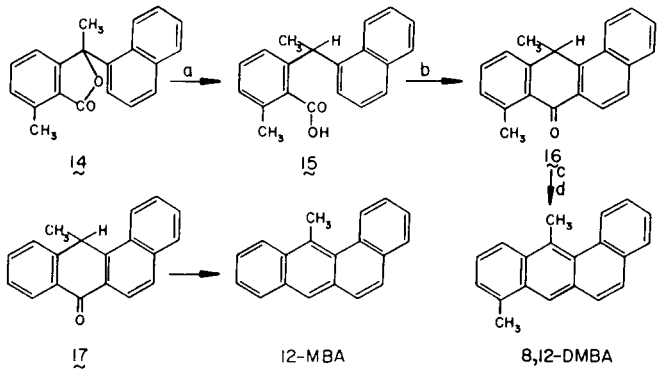
Instead of separating mixtures of acids as shown in Scheme II it is possible to convert mixtures of hindered and unhindered acids into mainly hindered or unhindered acids. For example, when a mixture

of **7** and **8** (where R = Cl) in 96% sulphuric acid was held at 120–125°C for 15 min and poured on to ice, an 83% yield of almost pure **7** was obtained when the alkali-soluble portion of the products was isolated (Newman *et al.*, 1986). Alternatively, when a mixture of **3** and **4** (R = CH_3, rich in **3**) was heated with 80% sulphuric acid at 85–90°C for 30 min, acid **4** was obtained in 75% yield on crystallization of the products (Newman, 1983). The latter method of isomerization to the unhindered acid was developed in the anthracene series by Cristol and Casper (1968). For explanations of the isomerization of **3** to **4** and of **8** to **7**, see a discussion of the Hayashi rearrangement (Section 1.4).

The yield of mixtures of acids, such as **3** and **4**, can often be increased if the 1-naphthylmagnesium bromides used are prepared from pure sublimed magnesium activated by ethylene dibromide (Pearson *et al.*, 1959), and phthalic anhydride (Newman and Tuncay, 1980).

With pure ketoacids of desired structure the introduction of methyl groups at positions 7- and/or 12- can be accomplished in several ways. For example, reaction of **3** (R = CH_3) with methylmagnesium bromide gave the lactone **14** which on reduction yielded the acid **15**. Cyclization of **15** afforded the benzanthrone **16** which was immediately reduced and the resulting alcohol (not isolated) dehydrated to 8,12-DMBA (Newman, 1937), Scheme III.

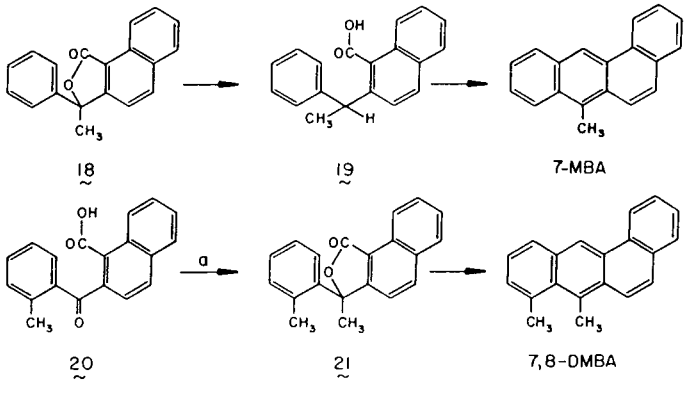
Scheme III. Synthesis of 12-MBAs.



When the acid **3** (R = H) was similarly treated 12-MBA was produced via the anthrone **17** (Newman, 1937). When the acid **7** (R = H) was reacted with methylmagnesium iodide the lactone **18** was obtained. Reduction furnished the acid **19**, which was cyclized to the benzanthrone

and thence to 7-MBA (Fieser and Newman, 1936; Cook *et al.*, 1937). Use of ketoacid **20** in an identical sequence of reactions yielded 7,8-DMBA (Fieser and Newman, 1936), Scheme IV. An unusual base-pro-

Scheme IV. Synthesis of 7-MBAs



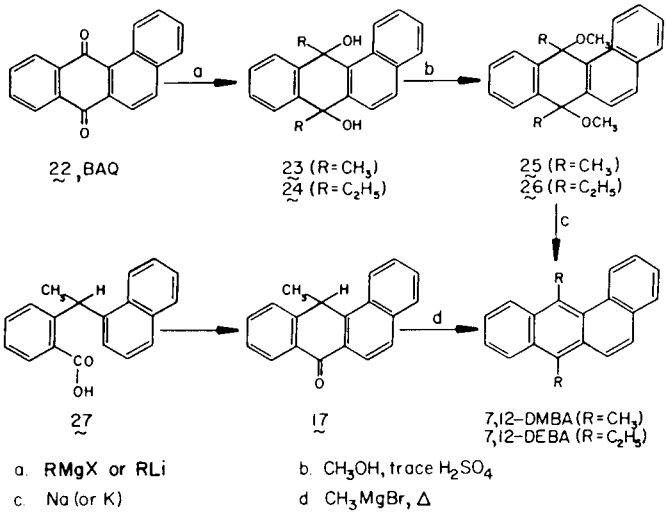
a. CH_3MgX.

moted cyclization occurred when *o*-(naphthylmethyl)benzoic acid was treated with phenyllithium to yield 7-PhBA (Bradsher and Webster, 1958). No other example of such a cyclization has been observed.

The syntheses of 7,12-DMBA types have been accomplished by a wide variety of methods. The reaction of benz[a]anthracene-7,12-dione, BAQ, **22**, with methylmagnesium bromide (or ethylmagnesium bromide) yielded **23** (or **24**). All early attempts to convert **23** to 7,12-DMBA with acid reagents failed (Bachmann and Chemerda, 1938). However, treatment of **23** with acidic methanol for a short time gave the dimethyl ethers **25** and **26**. Subsequent treatment of **25** and **26** with two equivalents of finely powdered sodium (or potassium) afforded 7,12-DMBA and 7,12-DEBA in high yields (Bachmann and Chemerda, 1938), Scheme V. By this method 8,9-DMBAQ was converted into 7,8,9,12-TeMBA (Badger *et al.*, 1940) and 11-MBAQ into 7,11,12-TMBA (Newman, 1983). However, reaction of 7,12-dimethoxy-7,12-dihydro-2,7,12-TMBA with sodium did not yield 2,7,12-TMBA (Defay and Martin, 1955). The anthrone **17**, obtained from **27**, on treatment with methylmagnesium bromide yielded 7,12-DMBA (Newman, 1938*a*). A number of 7-alkyl-12-MBAs was prepared from **17** (Mikhailov and Chernova, 1938).

Later 7,12-DMBA was synthesized by adding **23** directly to a solution of hydriodic acid in methanol to yield 7-iodomethyl-12-MBA, **28**, which

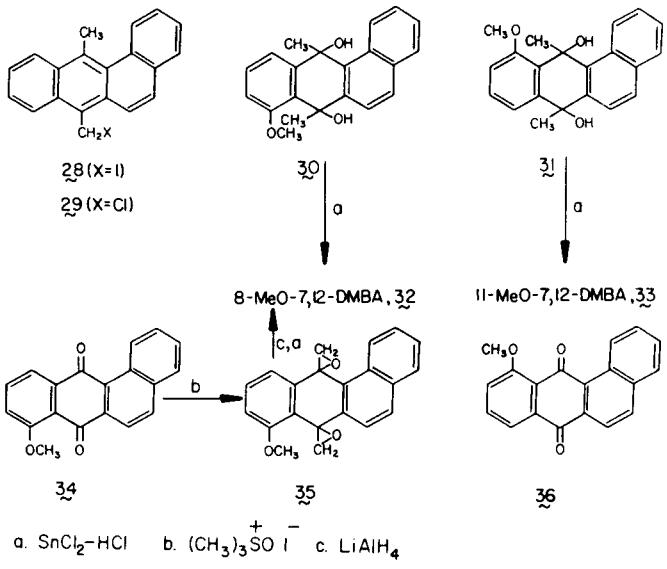
Scheme V. Synthesis of 7,12-DMBAs.



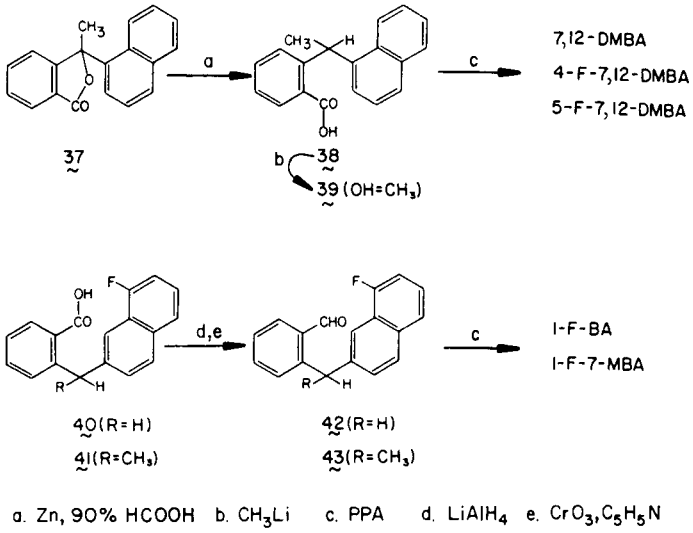
was immediately reduced in high yield to 7,12-DMBA by treating with stannous chloride and hydrochloric acid (Sandin and Fieser, 1940). Since the iodomethyl derivatives, **28**, are not too stable, syntheses of 7,12-DMBAs were improved by reacting **23** with dry HCl (instead of HI) to obtain the more stable **29** in high yields (Newman and Sankaran, 1977). Reduction of **29** by $SnCl_2$-HCl (Sandin and Fieser, 1940), was quantitative. However, when this two-step conversion of **23** to 7,12-DMBA was tried with **30** and **31** only tars resulted (Newman and Kanakarajan, 1980). Yet, when **30** and **31** were treated with a solution of $SnCl_2$ and HCl in ethyl acetate, high yields of 8-MeO-7,12-DMBA, **32**, and 11-MeO-7,12-DMBA, **33**, were produced (Newman and Kanakarajan, 1980). Interestingly, good yields of **30** and **31** could not be obtained by treating 8-MeO-BAQ, **34**, and 11-MeO-BAQ, **36**, with methylmagnesium iodide or methyllithium. However, when **34** was treated with the methylene reagent formed from trimethylsulphonium iodide (Corey and Chaykovsky, 1965; McCarthy *et al.*, 1978; Newman and Kanakarajan, 1980), an excellent yield of **35** was obtained. Subsequent reduction with $LiAlH_4$ led to **30** in high yield. Transformation of **36** into **33** via **31** was accomplished likewise with similar results (Newman and Kanakarajan, 1980), Scheme VI.

Improvements on the ketoacid route to 7,12-DMBA (Newman, 1938*a*) have been made (Scheme VII). Reduction of the phthalide **37** with 90% formic acid and zinc dust gave **38** in 97% yield (Letsinger *et al.*, 1961). The fact that reduction of a lactone similar to **37** but having methoxy

Scheme VI. Synthesis of 8- and 11- Methoxy-7,12-DMBAs.



Scheme VII. Synthesis of BAs.



groups in the 3- and 4-positions of the naphthyl moiety went in almost quantitative yield (Newman and Davis, 1967), indicates that the formic acid method of reduction works well with compounds that are often sensitive to acid reagents. Conversion of **38** to the methyl ketone **39** was effected in 75% yield with methyllithium and ring closure to 7,12-DMBA was achieved in 87% yield by heating for 1 h at 95°C with polyphosphoric acid (PPA) (Newman and Naiki, 1962). Similarly 4-F- and 5-F-7,12-DMBAs were made from the appropriate fluorinated intermediates (Newman and Naiki, 1962).

Often in the conversion of acids such as **38** to methyl ketones by treatment with methyllithium the yields were higher if the methyllithium reagent was prepared from methyl iodide rather than methyl bromide (Newman and Cunico, 1972).

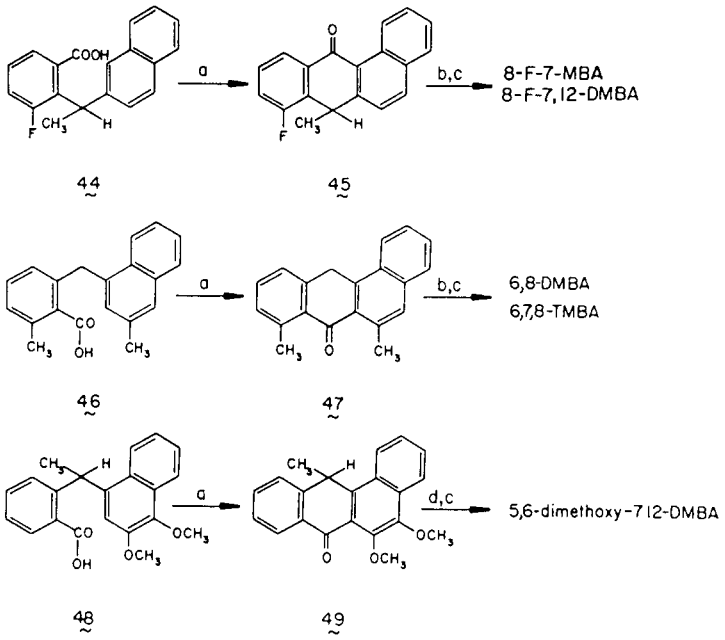
In a modification to avoid cyclization of an acid to a benz[a]anthrone followed by reduction and dehydration to a BA compound, the acids **40** and **41** were converted into the aldehydes **42** and **43** by first reducing the acids to primary alcohols with $LiAlH_4$ followed by oxidation with chromic oxide in pyridine at 20°C (Poos *et al.*, 1953). PPA cyclization of the aldehydes gave 1-FBA and 1-F-7-MBA in good overall yields (Newman and Seshadri, 1962). The oxidation of primary alcohols to aldehydes has also been accomplished (Newman *et al.*, 1983), by the N-chlorosuccinimide-dimethyl sulphide reagent (Corey and Kim, 1972). Similar uses of aldehydes were involved in the syntheses of 5-F-6,8-DMBA (Newman *et al.*, 1972), 5-FBA (Newman and Din, 1971), and 5-Br-12-MBA (Newman and Hussain, 1982).

Benz[a]anthrones have been made from acids such as **19** and **27** by treatment with acidic cyclization reagents. The use of anhydrous HF appears to be the best in that anthrones are easily isolated in high yields in the cases of **44**, **46** and **48** shown in Scheme VIII (Fieser and Hershberg, 1939, 1940; Newman and Blum, 1964*a*,*b*; Newman and Davis, 1967; Pataki and Balick, 1977).

1.2 Organometallic intermediates

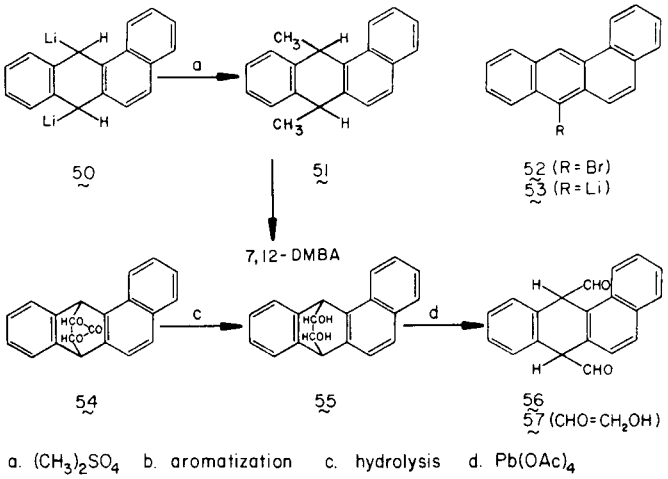
Additional ways to convert BA into 7,12-DMBA, shown in Scheme IX, involved reaction of BA with lithium or sodium to yield 7,12-dimetallated derivatives, **50**, which were reacted with methylating agents to yield 7,12-dihydro-7,12-DMBA, **51**. These could then be aromatized to BA compounds (Mikhailov, 1946; Mikhailov and Kozminskaya, 1947; Mikhailov and Blokhina, 1949*a*,*b*; Mikhailov, 1950). When 7-BrBA, **52**, was treated with butyllithium, 7-lithioBA, **53**, was formed and on reaction with carbon dioxide, methyl iodide, and ethyl iodide,

Scheme VIII. Benzanthrone Route to BA Compounds.



a HF b. reduction or CH_3MgX c. dehydration d. CH_3MgX

Scheme IX. Lithiation of BA.



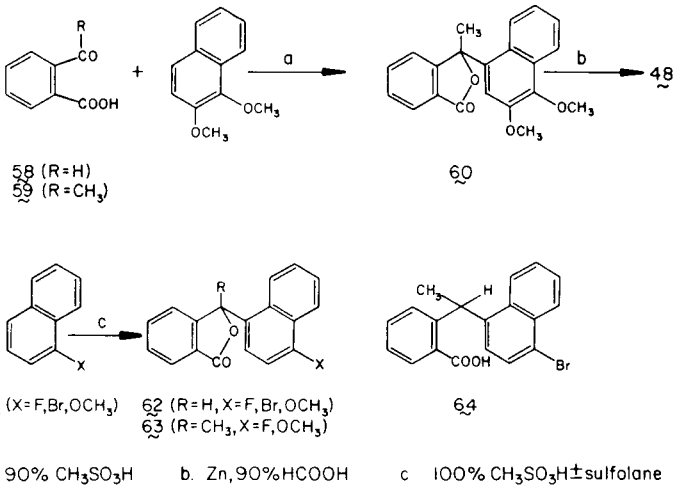
a. $(CH_3)_2SO_4$ b. aromatization c. hydrolysis d. $Pb(OAc)_4$

7-carboxyBA, 7-MBA and 7-EBA were obtained, respectively (Mikhailov and Kozminskaya, 1948, 1951).

When BA was reacted with vinylene carbonate (Newman and Addor, 1955), a good yield of adduct, **54**, was obtained. Hydrolysis gave the corresponding diol, **55**, which on treatment with lead tetraacetate furnished 7,12-dialdehydo-7,12-DHBA, **56**. Conversion of **56** into 7,12-bishydroxymethyl-7,12-DHBA, **57**, followed by reduction and dehydrogenation yielded 7,12-DMBA. Similarly, 5-FBA was converted into 5-F-7,12-DMBA (Newman and Din, 1971).

In the routes to BA derivatives outlined in Schemes I–VIII, the two carbons which end up in the meso positions of BA come from the two carbonyl groups in the phthalic anhydride or 1,2-naphthalic anhydride. The same is true of another route which starts with phthalaldehydic acid, **58**, or *o*-acetylbenzoic acid, **59**. The synthesis of the acid **48** began with the condensation of **59** with 1,2-dimethoxynaphthalene to yield 3-methyl-3-(3,4-dimethoxy-1-naphthyl)phthalide, **60**, which was then reduced to **48** (Newman and Davis, 1967), Scheme X. Later both **58**

Scheme X. Condensation of Phthalaldehydic and o-Acetylbenzoic Acids.



and **59** were condensed with naphthalene and 1-substituted naphthalenes, **61**, to yield the substituted phthalides, **62**, **63** (Newman *et al.*, 1975). None of the expected phthalide was obtained when **59** was reacted with **61** (X = Br). However, the desired bromoacid, **64**, was made in high yield by bromination of **38** (Scheme VII) (Newman and Cunico, 1972).