THE JOURNAL OF Organic Chemistry®

VOLUME 29, NUMBER 8

AUGUST 12, 1964

1-Methyl-7-halo-2-naphthalenecarboxylic Acid Derivatives

RODGER W. GRIFFIN, JR.,[1a] JERALD D. GASS, MARTIN A. BERWICK,[1b] AND RICHARD S. SHULMAN[1b]

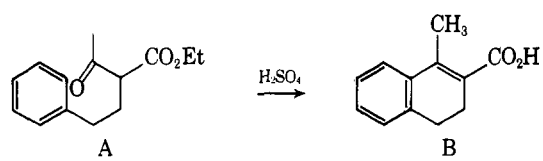
Department of Chemistry, Harvard University, Cambridge 38, Massachusetts, and Department of Chemistry, University of California, Berkeley 4, California

Received February 21, 1964

β-(*p*-Bromo and *p*-chlorophenyl)ethyl acetoacetic esters (**6**) were cyclized with cold concentrated sulfuric acid affording the respective 1-methyl-2-carboxy-7-halo-3,4-dihydronaphthalenes (**7**) which were esterified and then aromatized with bromine to the naphthalene compound. Studies of the condition of the ring-closure reaction are reported. Reduction of the naphthalene ester and subsequent treatment with phosphorous tribromide afforded 1-methyl-7-halo-2-bromomethylnaphthalenes (**11**). 7-Bromo-1-tetralone (**12**) was converted to the corresponding 2-carboxylic acid (**13**) and 2-carboethoxy ester (**16**), but attempts to introduce the 1-methyl group failed.

One difficulty in the preparation of polyfunctional naphthalenes from naphthalene and mono- and disubstituted naphthalenes is the myriad of possible products with similar properties which may be formed. The more acute problem arises in those cases where a *particular isomer* cannot be readily synthesized in good yield and a high degree of purity by using any combination of simple, available naphthalene starting materials and employing known reaction sequences.[2] This is the situation for the 1-methyl-7-halo-2-naphthalenecarboxylic acids and their derivatives.

The key step in the present ten-step syntheses is a modification of the van Auwers[3] ring closure of β-



A B

phenethylacetoacetic ester (A), which affords 1-methyl-3,4-dihydronaphthalene-2-carboxylic acid (B). The conditions and variables for the reaction have been studied here; the yields have been substantially increased. The reactions were initially carried out using the β-(*p*-chlorophenyl) compound, but, when the prepared material had been consumed, we turned to the synthesis of the corresponding bromo isomers. Finally, a carboxyl group was introduced into the 2-position of 7-bromo-1-tetralone; however, further transformations did not appear promising and the ring-closure reactions are preferred for obtaining the desired 1,2,7-trisubstitution pattern.

Synthesis of 7-Bromo- and 7-Chloro-3,4-dihydronaphthalene-2-carboxylic Acids (I).—*p*-Bromobenzyl bromide (1 Br) and *p*-chloroacetonitrile (2 Cl) are the commercially available starting materials for these two sequences. Compounds 2 Br, **3**, **4**, and **5** were prepared in good to excellent yields by slight modifications of standard procedures. An attempt to prepare bromide **5** using phosphorous tribromide led to lower yields of less pure product. The alkylation reaction (**5** → **6**) in the bromo series was modified from run to run (see Experimental), but the product was consistently obtained in only 45–55% yield.

The conditions of the sulfuric acid ring-closure reaction were critical in terms of obtaining maximum yields. A study of the various factors is set forth in Tables I and II for the chloro and the bromo series. Several attempts to use polyphosphoric acid failed. Even the maximum yield shown for the chloro compound (expt. 43) surely does not reflect the optimum conditions which might be found; our later experience with the bromo series indicates the use of still longer reaction times. When the reactants (ester **6** and concentrated sulfuric acid) are mixed at low temperature, there is formed an immediate yellow, orange, or red color, and, in general, the higher the ratio of sulfuric acid, the lighter the initial color. In all cases where it was sought, at least some starting material was recovered, although often only a few tenths of a per cent. This ester could be subjected again to the conditions of the cyclization reaction and additional acid obtained. Aromatic sulfonation is a slow competitive reaction which

(1) (a) To whom inquiries may be directed at the University of California; (b) National Science Foundation Undergraduate Research Participants, summer, 1962.

(2) For example, see the excellent discussion of naphthalene and tetralone chemistry by E. H. Rodd and J. Van Alphen ("Chemistry of Carbon Compounds," Vol. IIIB, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1956, Chapter XX, pp. 1273–1348) and by N. Donaldson ("The Chemistry and Technology of Naphthalene Compounds," E. Arnold Publishers, Ltd., London, 1958).

(3) (a) K. van Auwers and K. Müller, *J. prakt. Chem.*, **104**, 124 (1925). (b) For the formation of cyclic ketones from acids, see W. S. Johnson, *Org. Reactions*, **2**, 114 (1944).

TABLE I

CYCLIZATION CONDITIONS FOR 1-METHYL-7-CHLORO-3,4-DIHYDRONAPHTHALENE-2-CARBOXYLIC ACID (7 Cl)

Expt. no.	Ratio H_2SO_4–ester (6)	% yield	Recovered ester (6), g.	% conversion	Comments
20	10.0	0	*a*		1 hr. at 0°
25	8.1	1	9.2		1 hr. at 0°
26	8.2	8	7.0	33	6 → 15° on mixing, cooled to 6°; total, 30 min.
27	7.9	52	2.6	83	4 → 13° on mixing, cooled to 10°, and allowed to warm to room temperature; total, 30 min.
30	8.0	55	0.7	65	25 → 40° on mixing; total, 30 min. at ambient temperatures
39	8.0	1	0.2	15	85 → 105° on mixing, stirred at 87° on steam bath for 30 min.
40	7.7	38	1.8	90	4 → 14° on mixing, cooled to 10°, and allowed to warm to room temperature; total, 30 min.
41	8.0	39	11.5	91	Same as 40
42A	8.0	31	10.4[b]	66[b]	Same as 40
42B	8.7	20	34.0	78	Same as 40
42C	8.8	40	18.8	89	Same as 40 except 1-hr. total
43	7.3	61	10.0	91	Same as 40 except 2-hr. total

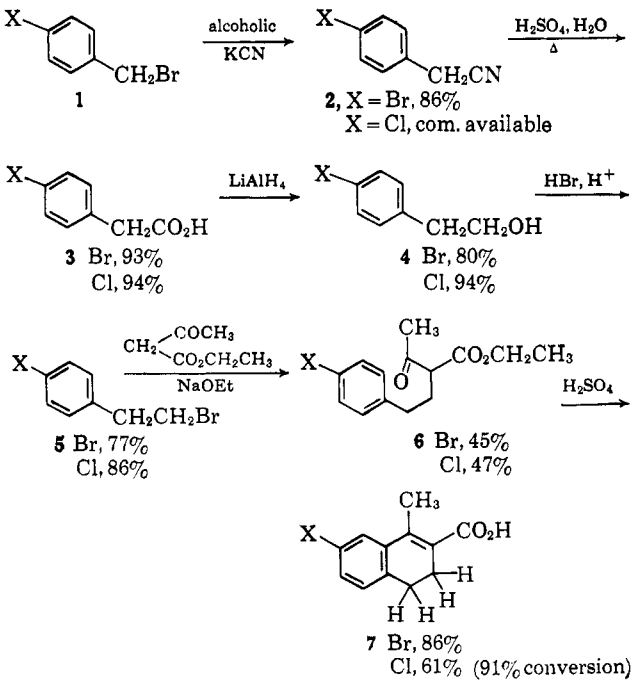
[a] No attempted isolation. [b] Represents minimum, some loss by spillage.

TABLE II

CYCLIZATION CONDITIONS FOR 1-METHYL-7-BROMO-3,4-DIHYDRONAPHTHALENE-2-CARBOXYLIC ACID (7 Br)

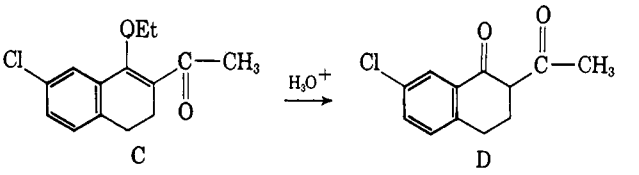
Expt. no.	Ratio H_2SO_4–ester (6)	Time, hr.	% yield	Recovered ester (6), g.	% conversion
42[a]	9.2	2.0	49	1.2	55
55[a]	10.2	1.0	17	16.6	58
56[a]	10.2	1.0	7	8.9	15
63	9.2	1.0	28	2.9	59
69	18.3	19.5	70	0.3	73
71	20.0	37.5	54	0.8	56
73	20.0	24.0	62	1.1	65
103	20.2	18.0	86	*b*	
115	9.2	19.5	68	0.3	72
119A	27.5	19.5	76	0.3	80
119B	37.6	19.5	73	0.1	75
125	27.6	19.5	77		

[a] These were early experiments carried out by one investigator; the remainder was performed by another. [b] No attempted isolation.

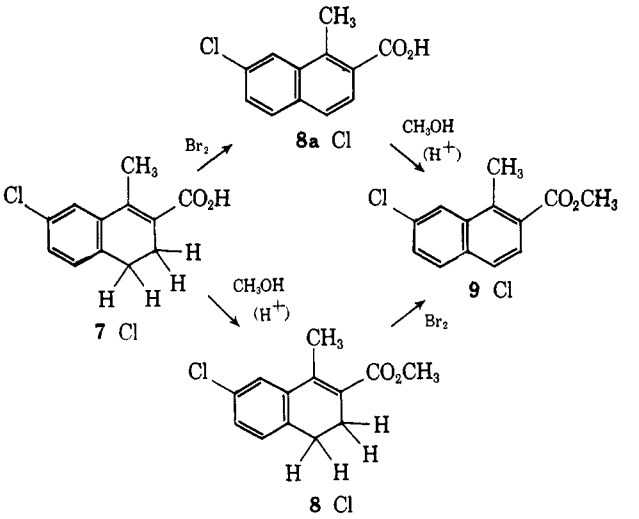


may account, at least in part, for the loss of material. Although the yield has been significantly reduced between 18 and 19.5 hr. (expt. 103 and 69), the optimum yield might be obtained after shorter reaction times.

In addition to the analytical and spectral evidence (see Experimental) which has been obtained for the structure of acid **7**, it was shown that the product did not contain sulfur, thus ruling out sulfonic acids. Further, a negative iodoform test indicates that it is not the compound which would be obtained by ring closure of the ester carbonyl (C), nor its subsequent hydrolysis product, diketone D.

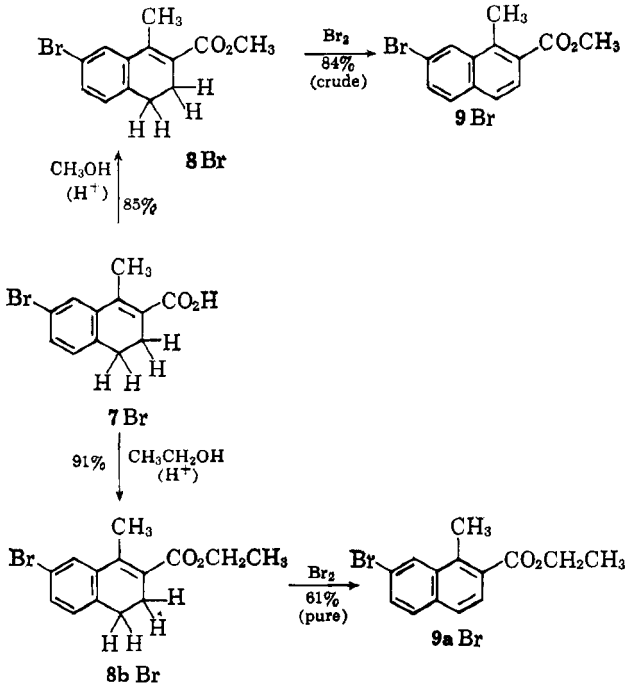


Aromatization and Naphthalene Derivatives.—The oxidation of the 3,4-dihydronaphthalenes was accomplished by treating a warm solution of the compound with bromine in carbon tetrachloride. In the chloro series, this was carried out both with the acid (**7** Cl) and

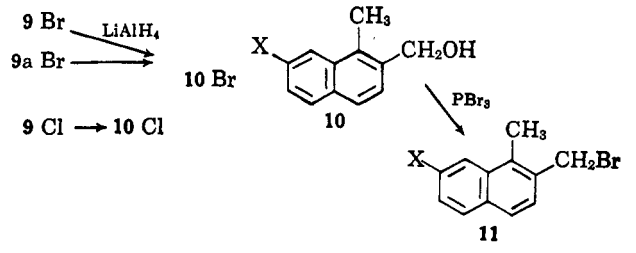


with the corresponding methyl ester (**8** Cl). Acid **7** Cl was extremely insoluble in carbon tetrachloride; however, ester **8** Cl was quite soluble and readily underwent aromatization. The compounds (**9** Cl) prepared by these two routes were identical.

Having established that the aromatization could be readily effected using the ester, both the methyl (**8** Br) and the ethyl esters (**8b** Br) were prepared in the bromo series and were smoothly aromatized. The higher melting 3,4-dihydroethyl ester (**8b** Br) was more readily purified and is to be preferred. Neither of these aromatized compounds, however, gave completely satisfactory elemental analyses despite repeated attempts at purification. Spectral data were consistent with these structures and further chemical transformations (*vide infra*) served to establish the structures.



The naphthalene esters in both series were reduced to the corresponding hydroxymethyl compounds (**10**) with lithium aluminum hydride and subsequently converted with phosphorous tribromide to the respective 1-methyl-2-bromomethyl-7-halonaphthalene (**11**). In the bromo series, reduction of the methyl and of the ethyl esters afforded products which were identical.

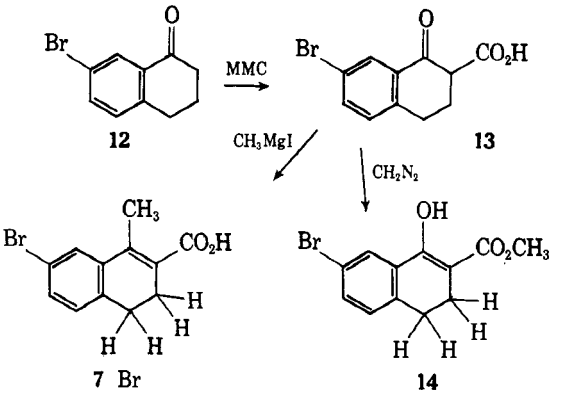


Attempts *via* 7-Bromo-1-tetralone (12).—Introduction of a carboxyl group into the 2-position of 7-bromo-1-tetralone (**12**) may be accomplished by at least two direct methods which utilize the activated methylene of 1-tetralones: (a) the use of methylmagnesium carbonate,[4] and (b) the alkylation with diethyl oxalate, followed by decarbonylation.[5] Both methods have been successful in our hands, and a few Grignard reactions of these compounds were attempted.

7-Bromo-1-tetralone (**12**) has been synthesized by the succinoylation of bromobenzene, followed by Clemmensen reduction and subsequent ring closure, using improved modifications of the procedures described previously.[6] The over-all yield has been increased to 50% employing a direct ring closure of the acid.

The conditions of this polyphosphoric acid (PPA) ring closure were most critical[7,8] and, consequently, were studied in some detail in order to obtain maximum yields of ketone **12**. The best yield in these experiments was obtained by mixing the starting material with PPA at 40° and maintaining the temperature at 75° for 35 min. (63% yield), but this was nearly the same as starting at 40°, maintaining the mixture at 70° for 10 min., and finally at 80° for 20 min. (61% yield). The lowest yield (39%) was obtained by heating the mixture at 80° for 7 min.

Ketone **12** was added to a solution of methylmagnesium carbonate (MMC) in dimethylformamide (DMF) and β-keto acid **13** was obtained in 27–57% yields (40% average). The compound is *extremely* susceptible to decarboxylation not only on storage in a dry atmosphere but especially in solution (*vide infra*). Preparation of



methyl ester **14**, using diazomethane in cold ether, proceeded in poor yield (31%), and a considerable amount of starting ketone **12** was obtained as a result of decarboxylation. However, the methyl ester was stable and easily handled.

Treatment of acid **13** with methylmagnesium iodide led to the isolation of only traces of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (**7** Br), and, again, considerable quantities of ketone **12** were produced. The instability of acid **13** and the poor yields of acid **7** Br dictated the route employing diethyl oxalate.

The glyoxalyl derivative **15** was prepared in yields of 50–70% using diethyl oxalate and sodium ethoxide. The bright yellow, α,γ-diketo ester **15** was stable and underwent a ready decarbonyation over soft glass at 180–185° in 85–90% yields. The n.m.r. spectrum indicates that β-keto ester **16** exists predominantly in the enol form under these conditions ($CDCl_3$) and the enol

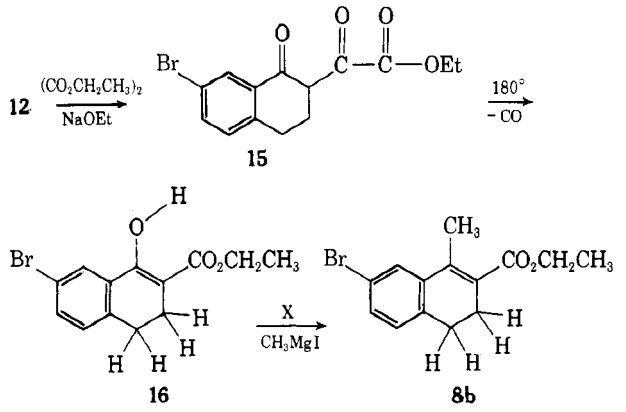
(4) M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

(5) For a general discussion, see C. R. Hauser, F. W. Swamer and J. T. Adams, *Org. Reactions*, **8**, 116 (1954). For a specific example, see H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 251.

(6) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

(7) J. Koo, *ibid.*, **75**, 1891 (1953).

(8) H. R. Snyder and F. X. Werber, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 798.



proton is found at τ −2.45 at 60 Mc.[9] Treatment of ester **16** with methylmagnesium iodide (inverse addition) gave immediate gas evolution and afforded none of the desired 3,4-dihydronaphthalene **8b** Br; 77% of the starting material was recovered unchanged.

Experimental[10]

The Chloro Series. *p*-Chlorophenylacetic Acid (3 Cl).—This is a modification of the hydrolysis of phenylacetonitrile.[11] A mixture of 210 ml. of concentrated sulfuric acid, 280 ml. of water, and 226.7 g. (1.49 moles) of *p*-chlorophenylacetonitrile (Eastman Kodak, No. P-6947, m.p. *ca.* 28–30°) was heated under reflux with stirring for 3 hr. The reaction mixture was poured with stirring into 1 l. of cold water and the entire suspension was treated with sufficient ether to dissolve the solids. The aqueous layer was repeatedly extracted with ether and the combined organic layer was dried and evaporated affording 243.9 g. of *p*-chlorophenylacetic acid (96% yield) as white crystals, m.p. 102–106°. A small sample was recrystallized twice from ether–petroleum ether (b.p. 30–60°), raising the melting point to 106–107° (lit.[12] m.p. 104–105°).

2-(*p*-Chlorophenyl)ethanol (4 Cl).—A solution of 107.4 g. (0.614 mole) of *p*-chlorophenylacetic acid (**3** Cl) in 400 ml. of dry ether (distilled from *n*-butylmagnesium bromide) was added dropwise over a period of 2 hr. to a stirred mixture of lithium aluminum hydride (38 g., 1.0 mole) in 800 ml. of dry ether. Refluxing was continued for 1 hr., the mixture was cooled to room temperature, and the excess hydride was decomposed by the dropwise addition of methanol. Ice and dilute hydrochloric acid were then added, the layers were separated, and the aqueous layer was extracted several times with ether. The combined ether extracts were washed with water, dried, and evaporated.

The remaining oil was distilled at reduced pressure affording 93.2 g. (94% yield) of colorless 2-(*p*-chlorophenyl)ethanol in those fractions which distilled at 144–153° at 30–34 mm. (lit.[13] 166° at 47.2 mm.).

The reaction was run several times and the yields were generally about 90%. Other values were obtained for the distilling range: 163–165° at 44.5 mm. and 127–129° at 9 mm.

2-(*p*-Chlorophenyl)bromoethane (5 Cl).—To a stirred mixture of 60 ml. of 48% hydrobromic acid and 15 ml. of concentrated sulfuric acid was added over a period of 5 min. 58.9 g. (0.376 mole) of 2-(*p*-chlorophenyl)ethanol (**4** Cl). An additional 10 ml. of concentrated sulfuric acid was added and the mixture was heated under reflux for 3 hr. The mixture was cooled to room temperature and poured over ice. The layers were separated and the aqueous solution was extracted with several portions of ether. The combined ether extracts were successively washed with water, dilute sodium bicarbonate, and water, and then dried and evaporated.

The resulting oil was distilled at reduced pressure and the fractions collected at 114–123° at 7 mm. afforded 70.7 g. (86% yield) of 2-(*p*-chlorophenyl)-1-bromoethane (**5** Cl) as a colorless oil, (b.p. 133° at 15 mm.)

Anal. Calcd. for C_8H_8BrCl: C, 43.77; H, 3.67; total halogen, 52.55. Found: C, 43.94; H, 3.79; total halogen, 52.38.

The yield in this reaction was generally 70–80%; however, treatment of the alcohol with phosphorus tribromide afforded the corresponding bromide in only 50–55% yield.

3-Carbethoxy-5-(*p*-chlorophenyl)pentanone-2 (6 Cl).—To a stirred solution of sodium ethoxide (prepared from 17 g. (0.74 g.-atom) of sodium in 400 ml. of absolute ethanol) was added 97 g. (0.745 mole) of ethyl acetoacetate followed by the dropwise addition of 134.5 g. (0.613 mole) of 2-(*p*-chlorophenyl)-1-bromoethane (**5** Cl). The mixture was heated under reflux for 6 hr. and then allowed to stand at room temperature with stirring for *ca.* 30 hr. Water and dilute hydrochloric acid were added, the layers were separated, and the aqueous layer was washed with ether. The combined ether portion was successively washed with water, dilute sodium bicarbonate, and water. (Acidification of the bicarbonate washings gave a negligible precipitate.) The ether was dried and removed and the resulting oil was distilled at reduced pressure.

The fraction distilling at 140–160° (most at 155°) and 1.5 mm. was collected and represents 164.5 g. (47% yield) of 3-carbethoxy-5-(*p*-chlorophenyl)pentanone-2. The material was redistilled twice (138.5–139° at 0.5–0.7 mm. and 139.5–140° at 0.8 mm.). The infrared spectrum (CCl_4) showed peaks at 5.77 and 5.70 (shoulder) μ (C=O).

Anal. Calcd. for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.38; Cl, 13.19. Found: C, 62.70; H, 6.19; Cl, 13.21.

1-Methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (7 Cl).—This reaction was carried out many times (see Table I) and these directions represent the case of maximum yield (expt. 43), although not necessarily the optimum conditions.

Concentrated sulfuric acid (240 g.) and 33.29 g. (0.124 mole) of 2-carbethoxy-5-(*p*-chlorophenyl)pentanone-2 (**6** Cl) were separately cooled to 4° and the ester was then added to the sulfuric acid. Although the temperature rose, the mixture was swirled in the ice bath until the temperature had dropped to 10°. The flask was removed from the bath and allowed to come to room temperature. After 2-hr. total reaction time, the mixture was poured onto ice, ether was added, the layers were separated, and the aqueous portion was extracted with ether. The combined organic layer was washed with water and subsequently with 10% sodium hydroxide.

The sodium hydroxide layer was acidified with dilute hydrochloric acid and extracted with several portions of ether. The dried ether was evaporated, affording 16.94 g. (61% yield) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (**7** Cl) as a white solid.

A sample was recrystallized successively twice from benzene–petroleum ether, once from ether–petroleum ether, and twice from benzene, affording white crystals, m.p. 212–212.5°.

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.74; H, 4.64; Cl, 15.721.

The ether solution which had been extracted with base was dried and evaporated affording 9.96 g. of an oil, whose infrared spectrum was identical with that of starting material. This represents a 91% conversion to the dihydronaphthalene compound. The oils thus recovered were cyclized with sulfuric acid affording additional product: $\lambda_{max}^{95\%\ EtOH}$ 228 (log ϵ 4.31), 278 (4.05), and 304 (shoulder) mμ (3.77).

1-Methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (7 Cl).—A mixture of 10.79 g. (0.49 mole) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (**7** Cl), 300 ml. of absolute

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," International Series Monographs on Organic Chemistry, Vol. V, Pergamon Press, London, 1959, p. 71.

(10) Melting points are uncorrected and were taken at 1°/min. (or less) on a Fischer-Johns apparatus. The spectra were recorded as follows: infrared, Perkin-Elmer Model 21, fitted with sodium chloride optics, and Perkin-Elmer Infracord; ultraviolet, Cary recording spectrophotometer and with the Perkin-Elmer Model 202; n.m.r., Varian Associates Model A-60, usually as a dilute solution in chloroform-*d* and tetramethylsilane (TMS) (internal standard). It has been our standard practice to distil tetrahydrofuran (THF) twice from lithium aluminum hydride (pre-drying over anhydrous calcium chloride if necessary). The second distillation is usually carried out under an atmosphere of dry nitrogen. Solvents for infrared and n.m.r. spectral determinations are always dried immediately before use by passing them through a capillary dropping tube containing a few grams of alumina, usually Woelm, activity grade I. The addition of decolorizing charcoal to organic solutions of crude compounds still containing a drying agent greatly aids later purification by distillation or crystallization. Anhydrous magnesium sulfate was used throughout as the drying agent.

(11) R. Adams and A. F. Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 436.

(12) F. Beilstein and A. Kuhlberg, *Ann.*, **147**, 346 (1868).

(13) R. R. Dreisbach and S. A. Shroder, *Ind. Eng. Chem.*, **41**, 2879 (1948).

methanol, and 6 ml. of concentrated sulfuric acid was heated under reflux for 8 hr. and allowed to stand overnight at room temperature. Water was added and the mixture was extracted with several portions of ether. The combined ether extracts were washed successively with water, 10% sodium hydroxide, water, 5% hydrochloric acid, and water, and then dried. The ether was taken to dryness affording 10.56 g. (93% yield) of 1-methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (**8** Cl) as a white solid, m.p. 50–51.5° after recrystallization from petroleum ether.

An analytical sample was successively recrystallized once from *n*-hexane, once from ether, and three times from petroleum ether. The sample melted at 51–52°.

Anal. Calcd. for $C_{13}H_{13}ClO_2$: C, 65.96; H, 5.54; Cl, 14.98. Found: C, 65.81; H, 5.73; Cl, 14.86.

This ester was also prepared from diazomethane in lower yields. The infrared spectra of the methyl esters prepared by these two methods were identical.

1-Methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) *via* the 3,4-Dihydronaphthalene Ester (8 Cl).—To a boiling solution of 7.51 g. (0.032 mole) of 1-methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (**8** Cl) in 100 ml. of carbon tetrachloride was added slowly 10 ml. of carbon tetrachloride solution containing 0.045 mole (6 ml.) of bromine. After the addition, the solvent was removed *in vacuo* and the resulting solid was recrystallized several times from ether–petroleum ether and again from methanol affording 1-methyl-2-carbomethoxy-7-chloronaphthalene (**9** Cl) as white crystals, m.p. 86–87.5°. The following spectral properties were found: infrared (CCl_4), 5.81 μ (C=O); ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 233 (log ϵ 4.74), 243 (4.69, shoulder), 274 (3.90), 284 (3.91), and 295 mμ (3.72); n.m.r. (CCl_4), C_1–CH_3, τ 7.23 (singlet), $-CO_2CH_3$, τ 6.12 (singlet), Ar-C_8-H, τ 2.00 (singlet), and other Ar-H at τ 2.31–2.65 (complex multiplet, maximum at τ 2.47).

Anal. Calcd. for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.73; Cl, 15.11. Found: C, 66.13; H, 4.58; Cl, 14.87.

1-Methyl-2-carboxy-7-chloronaphthalene (8a Cl).—To a boiling slurry of 10.33 g. (0.046 mole) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (**7** Cl) in 300 ml. of carbon tetrachloride was added 11 ml. of a carbon tetrachloride solution containing 0.050 mole of bromine. Fumes of HBr were evolved. The mixture was cooled in an ice bath and filtered affording a solid, m.p. 210–230° after recrystallization several times from toluene.

A portion of this solid was refluxed with 100 ml. of 10% sodium hydroxide for 4 hr., acidified with hydrochloric acid, and filtered. The solid was recrystallized several times from toluene and from benzene–toluene, affording 1-methyl-2-carboxy-7-chloronaphthalene (**8** Cl) as a white solid, m.p. 242.5–244°.

Anal. Calcd. for $C_{12}H_9ClO_2$: C, 65.32; H, 4.11; Cl, 16.07. Found: C, 65.25; H, 4.41; Cl, 15.77.

1-Methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) *via* the Naphthoic Acid (8a Cl).—A mixture of 640 mg. (2.9 mmoles) of 1-methyl-2-carboxy-7-chloronaphthalene (**8a** Cl), 20 ml. of absolute methanol, and 0.5 ml. of concentrated sulfuric acid was heated under reflux for 6 hr. and allowed to stand overnight at room temperature. Crystals had formed in the flask and these were collected and recrystallized from ether affording 1-methyl-2-carbomethoxy-7-chloronaphthalane, m.p. 85–86.5°. Mixture melting point with a sample of the ester (m.p. 86–87.5°) prepared *via* the 3,4-dihydronaphthalene was 85.5–87°.

1-Methyl-2-hydroxymethyl-7-chloronaphthalene (10 Cl).—To a mixture of 1.2 g. (0.0316 mole) of lithium aluminum hydride in 75 ml. of dry ether (distilled from *n*-butylmagnesium bromide) which had been refluxed for 1 hr. was added, dropwise over a period of 0.5 hr., a solution of 5.91 g. (0.0251 mole) of 1-methyl-2-carbomethoxy-7-chloronaphthalene (**9** Cl) dissolved in 150 ml. of dry ether. The mixture was refluxed for 8 hr., allowed to cool to room temperature, and successively treated with ethyl acetate, methanol, ice, and sufficient 1:1 hydrochloric acid to dissolve the solids. The layers were separated and the aqueous portion was saturated with sodium chloride and extracted with ether. The combined organic portion was washed with saturated sodium chloride solution, dried, treated with charcoal, and taken to dryness, affording a white solid which gave 2.88 g. (55% yield) of 1-methyl-2-hydroxymethyl-7-chloronaphthalene (**10** Cl) after recrystallization from ether–petroleum ether. Two crystalline modifications were obtained depending on the conditions of the crystallization: rosettes, m.p. 96.5–97°, and flat needles which first melted at 83.5°, solidified, and remelted at 96.5–97°. The former were usually obtained from solutions which had been cooled overnight in the freezing compartment of a refrigerator; the latter precipitated from solution at room temperature. Further, a sample melting at 85° was allowed to stand in the cold and reverted to the 97° form.

A sample consisting of both crystalline forms was submitted for analysis and showed the following spectral properties: infrared (CCl_4), 2.78 μ (–OH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 232.5 (log ϵ 4.93) and 278 mμ (3.71, broad); n.m.r. (CCl_4), C_1–CH_3, τ 7.52 (singlet), $-C_2$–CH_2–, τ 5.14 (doublet, $J \sim 7$ c.p.s.), $-C_2$–CH_2–OH, τ 6.65 (broad multiplet), Ar-C_8-H, τ 2.97 (singlet), and other Ar-H at τ 2.1–2.75 (complex multiplet, maximum peak at τ 2.38).

Anal. Calcd. for $C_{12}H_{11}ClO$: C, 69.74; H, 5.37; Cl, 17.16. Found: C, 69.45; H, 5.33; Cl, 17.28.

1-Methyl-2-bromomethyl-7-chloronaphthalene (11 Cl).—A mixture of 1.988 g. (0.0097 mole) of 1-methyl-2-hydroxymethyl-7-chloronaphthalene (**10** Cl) and 8 g. (0.0295 mole) of phosphorous tribromide in 24 ml. of dry carbon tetrachloride was refluxed 6 hr. and then allowed to stand at room temperature for 24 hr. The solution was decanted from the small amount of acid (H_3PO_3) and poured into an equal volume of ice–water. The layers were separated and the organic portion was washed several times with ice–water, dried, filtered, and taken to dryness. The residue was recrystallized from ether–petroleum ether (charcoal) affording a total of 0.682 g. (26% yield) of 1-methyl-2-bromomethyl-7-chloronaphthalene (**11** Cl), m.p. 92–93°.

A sample was further recrystallized to m.p. 92.5–93°, submitted for analysis, and showed the following spectrum: n.m.r. (CCl_4), C_1–CH_3, τ 7.46 (singlet), $-C_2$–CH_2–Br, τ 5.45 (singlet), Ar-C_8-H, τ 2.12 (singlet), and other Ar–H at τ 2.30–2.87 (complex multiplet, maximum at τ 2.66).

Anal. Calcd. for $C_{12}H_{10}ClBr$: C, 53.46; H, 3.74; Cl, Br, 42.79. Found: C, 53.29; H, 3.85; Cl, Br, 42.90.

The Bromo Series. *p*-Bromobenzyl Cyanide (2 Br).—A mixture of 16.3 g. (0.251 mole) of potassium cyanide in 150 ml. of 95% ethanol and 65 ml. of water was heated to reflux and 49 g. (0.195 mole) of solid *p*-bromobenzyl bromide (**1** Br) was added in portions through the condensor over a period of 0.5 hr. An additional 50 ml. of 95% ethanol was used to wash the condensor. The mixture was refluxed for 30 min., 500 ml. of water was added, and the yellow oil, which solidified, was removed and recrystallized from 75 ml. of 95% ethanol (charcoal). After standing in the freezing compartment of a refrigerator overnight, 33 g. (86% yield) of *p*-bromobenzyl cyanide (**2** Br) was obtained (two crops), m.p. 47.5–48.5° (lit.[14] m.p. 50°). Many additional runs with a 45-min. reflux period were carried out on larger scale (250 g. of *p*-bromobenzyl bromide) and the *p*-bromobenzyl cyanide was consistently obtained in good yield (79–81%) and in high purity (m.p. *ca.* 47–49°).

***p*-Bromophenylacetic Acid (3 Br).**—A stirred mixture of 599.4 g. (3.06 moles) of *p*-bromobenzyl cyanide (**2** Br) in 650 ml. of concentrated sulfuric acid and 860 ml. of water was heated under reflux for 3 hr. and poured into 2.55 kg. of ice–water; the resulting white solid was collected by suction filtration, washed with fresh ice–water, and sucked for several hours at the water pump. The granular solids were dissolved in 2.5 l. of ether, dried (charcoal), filtered, concentrated to 1 l., diluted with 800 ml. of petroleum ether, swirled, and allowed to stand for 1 hr. in an ice–water bath. The solid was collected, washed with a little fresh cold solvent, air-dried for several hours, and finally dried overnight in a vacuum desiccator (P_2O_5). There was obtained 609.3 g. (92.5% yield) of *p*-bromophenylacetic acid (**3** Br) in two crops (593 g., 16.3 g.), each melting at 115.5–116° (lit.[14] m.p. 114°). On a smaller scale this reaction afforded similar yields, although the first crop was often more pure (*i.e.*, one melting at 117–118°).

2-(*p*-Bromophenyl)ethanol (4 Br.)—To a stirred mixture of 19 g. (0.50 mole) of lithium aluminum hydride in 350 ml. of dry ether (distilled from *n*-butylmagnesium bromide) was added dropwise, over a period of 75 min., a solution of 68.9 g. (0.31 mole) of *p*-bromophenylacetic acid (**3** Br) in 250 ml. of dry ether. The mixture was refluxed for 1 hr. and cooled in an ice–water bath; methanol was *cautiously* added dropwise until the visible evolution of hydrogen had ceased. Ice and dilute hydrochloric acid were added, the layers were separated, and the aqueous portion was extracted several times with ether. The combined ether extracts were washed with water, dried (Norit), and filtered. The ether was removed and the remaining colorless oil was fractionally distilled affording 50.78 g. (80% yield) of 2-(*p*-bromophenyl)-

(14) J. Frederick, *J. Chem. Soc.*, 161 (1934).

ethanol (**4** Br) as a colorless, viscous oil, distilling in the range 149–154° at 17–19 mm. (lit.[15] 143–150° at 7 mm.).

A portion was redistilled and the fraction collected at 154–155° at 18.5 mm. was submitted for analysis.

Anal. Calcd. for C_8H_9BrO: C, 47.79; H, 4.51; Br, 39.74. Found: C, 47.67; H, 4.60; Br, 39.71.

The yields were about 75–80% when the reaction was carried out on 250–350 g. of *p*-bromophenylacetic acid. Material distilling in the range of 148–154° at 13–15 mm. was collected and used directly in the following reaction, and had $n^{25}D$ 1.5700, infrared (CCl_4), 2.80 μ (–OH), and ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 221 mμ (log ε 4.00).

2-(*p*-Bromophenyl)bromoethane (5 Br.)—To a stirred mixture of 142 ml. (1.23 mole) of 48% HBr (b.p. 125°, colorless, distilled from anhydrous barium bromide), 41.4 ml. of concentrated sulfuric acid, and 179.7 g. (0.895 mole) of 2-(*p*-bromophenyl)-ethanol (**4** Br) was added an additional 25.2 ml. of concentrated sulfuric acid (dropwise). The mixture was refluxed with stirring for 3 hr. and then poured onto 500 g. of ice. (In some experiments, a cream-colored solid precipitated at this point; however, the product usually separated as an oil.) The layers (or solid) were separated, and the aqueous solution was extracted with ether. The combined organic portion (solid dissolved) was washed successively with water, 5% sodium bicarbonate, water, and saturated sodium chloride. The yellow ethereal solution was then dried (Norit) and concentrated *in vacuo* affording 208.9 g. (88% crude yield) of a yellow oil. Distillation of the oil at reduced pressure afforded 183.3 g. (77% yield) 2-(*p*-bromophenyl)-bromoethane (**5** Br) as a colorless, viscous oil distilling in the range 144–148.5° at 13–13.5 mm. (The main fraction often solidified, m.p. *ca.* 17°.)

A redistilled sample, collected in the range 124.5–125.5° at 5–5.5 mm., was submitted for analysis, and had $n^{25}D$ 1.5929 and ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 222 mμ (log ε 4.13).

Anal. Calcd. for $C_8H_8Br_2$: C, 36.40; H, 3.06; Br, 60.55. Found: C, 36.68; H, 3.12; Br, 60.37.

3-Carbethoxy-5-(*p*-bromophenyl)pentanone-2 (6 Br).—Into a three-necked 500-ml. round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and condenser (calcium chloride drying tube) was added with stirring 90 ml. of absolute ethanol and 3.01 g. (0.131 g.-atom) of freshly cut sodium metal. When the sodium had reacted, 17.03 g. (0.131 mole) of ethyl acetoacetate (freshly distilled, b.p. 43–46° at 3 mm.) was added, followed by the dropwise addition (10 min.) of 34.5 g. (0.131 mole) of 2-(*p*-bromophenyl)bromoethane (**5** Br). The temperature was gradually increased and a white solid (sodium bromide) separated from the pale green solution. The mixture was refluxed for 5 hr., allowed to stand at room temperature overnight, and then further refluxed for 30 min. The solution was transferred to a separatory funnel and treated with 4:1 hydrochloric acid; the lower layer (organic) was drawn off. The aqueous layer was treated with saturated sodium chloride and extracted with ether; the combined organic portion was successively washed with water, 5% hydrochloric acid, and water. The ethereal solution was dried (charcoal), filtered, and taken to dryness *in vacuo* affording 40.9 g. of a straw-colored oil which was fractionally distilled at reduced pressure: (a) 45–48° at 1 mm., 3.21 g. of ethyl acetoacetate; (b) 98–107° at 1.5 mm., 2.77 g. of 2-(*p*-bromophenyl)-bromoethane (**5** Br); (c) 142–155° at 1.5 mm., 18.22 g. of 3-carbethoxy-5-(*p*-bromophenyl)pentanone-2 (**6** Br); and (d) residue of 10.45 g. Fraction c represents 45% yield (48% yield based on recovered starting materials).

Redistillation afforded a clear, liquid sample [b.p. 149–150° at 1.5 mm.; $n^{25}D$ 1.5215; infrared (neat), 5.78 and 5.85 μ (C=O)] which was submitted for analysis.

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47; Br, 25.52. Found: C, 53.91; H, 5.57; Br, 25.40.

Several attempts were made to increase the yield in this reaction by taking extreme precautions, such as baking the apparatus overnight under nitrogen and carrying out the reaction under nitrogen which had been passed over copper at 500°, or by scrupulously drying the ethanol by the ethyl succinate method.[16] The yields, however, remained in the 48–55% range.

1-Methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br).—The reaction was carried out repeatedly and this procedure represents the experiment of maximum yield. Concentrated sulfuric acid (350 g.) and 17.26 g. (0.0530 mole) of 3-carboxy-5-(*p*-bromophenyl)-pentanone-2 (**6** Br) were each cooled to 3°. The ester was then added to the sulfuric acid dropwise with swirling at a rate such that the temperature did not rise above 5–6°. The mixture became yellow-orange almost immediately and after the addition had been completed the mixture was allowed to stand at room temperature for 18 hr. The red-orange solution was poured with stirring onto 1 kg. of ice and a white solid precipitated immediately. This was collected, washed, and dried *in vacuo* affording 12.7 g. (86% yield) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (**7** Br), m.p. 205–207°.

A sample [m.p. 215–215.5°[17]; infrared (KBr), 6.05 μ (–COOH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 228 (log ε 4.51), 275 (4.23), and 296 mμ (3.77, shoulder)] was recrystallized several times from ether–petroleum ether and submitted for analysis.

Anal. Calcd. for $C_{12}H_{11}BrO_2$: C, 53.95; H, 4.15; Br, 29.92. Found: C, 53.84; H, 4.34; Br, 29.86.

1-Methyl-2-carboxymethyl-7-bromo-3,4-dihydronaphthalene (8 Br.)—A mixture of 150 ml. of methanol, 3 ml. of concentrated sulfuric acid, and 4.87 g. (0.0182 mole) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (**7** Br) was refluxed for 12 hr., cooled to room temperature, diluted with water, and extracted with ether. The combined ethereal extract was successively washed with water, saturated sodium bicarbonate, 5% hydrochloric acid, and finally water. The ether was dried (charcoal) and taken to dryness affording 4.31 g. (85% yield) of 1-methyl-2-carboxymethyl-7-bromo-3,4-dihydronaphthalene (**8** Br) as a clear oil, which solidified on standing. A sample [m.p. 29–30°; infrared (CCl_4), 5.83 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 231 (log ε 4.45), 248 (small shoulder), 280 (4.06), and 310 mμ (3.67, broad)] was submitted for analysis after several recrystallizations from petroleum ether.

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.65; H, 4.42; Br, 28.39.

1-Methyl-2-carbomethoxy-7-bromonaphthalene (9 Br).—A solution of 2.81 g. (0.010 mole) of 1-methyl-2-carboxymethyl-7-bromonaphthalene (**8** Br) in 10 ml. of dry carbon tetrachloride was warmed and treated with a solution of bromine in carbon tetrachloride (0.001 mole/ml.) with intermittent warming and swirling. The bromine solution was added in small portions (*ca.* 1 ml.) and after a short induction period (2–3 min.), the bromine color was discharged fairly rapidly with the evolution of hydrogen bromide (total reaction time *ca.* 15–20 min.). The first 9 ml. (theoretical, 10 ml.) of bromine solution was taken up in a reasonable time (above) and the mixture was allowed to stand at room temperature for 0.5 hr. with an additional 0.5 ml. (9.5 ml. total) at which time the bromine color was still apparent.

The mixture was diluted with an equal volume of carbon tetrachloride, washed successively with water, 1% sodium bisulfite, 1% sodium bicarbonate, and finally dried (Nuchar). The filtered solution was taken to dryness *in vacuo*, affording 2.35 g. (84% yield) of 1-methyl-2-carboxymethyl-7-bromonaphthalene (**9** Br) as a white solid, m.p. 70.5–77°, softening at 69°.

Several samples [all with m.p. 81.5–82°; infrared (CCl_4), 5.79 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 234.5 (log ε 4.70), 247.5 (3.78), 284.5 (3.80), and 295 mμ (3.60); n.m.r. (CCl_4), C_1–CH_3, τ 7.12 (singlet), $-CO_2CH_3$, τ 6.05 (singlet), Ar-C_8-H, τ 1.65 (singlet), other Ar-H at τ 2.00–2.48 (complex multiplet, maximum peak at τ 2.32)] were submitted for analysis after various recrystallizations from petroleum ether.

Anal. Calcd. for $C_{13}H_{11}BrO_2$: C, 55.93; H, 3.97; Br, 28.63. Found: C, 55.90, 55.83, 55.21; H, 3.99, 3.76, 3.89; Br, 30.80, —, 30.38.

1-Methyl-2-carboxyethyl-7-bromo-3,4-dihydronaphthalene (8b Br).—A mixture of 250 ml. of absolute ethanol, 35 ml. of dry benzene, 10 ml. of concentrated sulfuric acid, and 10.04 g. (0.0375 mole) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (**7** Br) was refluxed for 24 hr. in a flask fitted with a Dean–Stark trap and condensor (calcium chloride drying tube). The solution was cooled to room temperature, diluted with 800 ml. of cold water, and extracted with ether. The combined organic extracts were washed successively with water, half-saturated sodium bicarbonate, water, and saturated sodium chloride, and then dried (Nuchar). The filtered light yellow solution was taken to dryness affording 10.08 g. (91% crude yield) of 1-methyl-2-carboxyethyl-

(15) L. Thielen and C. Dornfeld (to G. D. Searle and Co.), U. S. Patent 2,862,971 (Dec. 2, 1958). A mixture contaminated with undetermined amounts of *meta* and *ortho* isomers is reported to distil at 144.5–145° at 15 mm.: D. Sontag, *Ann. chim.*, [11]**1**, 359 (1934); *Chem. Abstr.*, **28**, 4717 (1934).

(16) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1957, p. 168.

(17) See also the preparation discussed under Tetralone Reactions.

7-bromo-3,4-dihydronaphthalene (**8b** Br) as a white solid (small amount of an adhering yellow oil). Recrystallization from 50 ml. of *n*-hexane (charcoal) afforded 7.06 g. (64% yield) of white crystals, m.p. 65–66°. Further recrystallizations from *n*-hexane afforded a sample [m.p. 66.5–67°; infrared (CCl_4), 5.84 μ (C=O)] which was submitted for analysis.

Anal. Calcd. for $C_{14}H_{15}BrO_2$: C, 56.96; H, 5.12; Br, 27.07. Found: C, 57.20; H, 4.97; Br, 26.92.

1-Methyl-2-carboxyethyl-7-bromonaphthalene (**9a Br**).—To a warm (not boiling) solution of 7.06 g. (0.0239 mole) of 1-methyl-2-carboxyethyl-7-bromo-3,4-dihydronaphthalene (**8b** Br) in 24 ml. of dry carbon tetrachloride was added (in 2-ml. portions) 24 ml. of 1 *M* bromine in carbon tetrachloride. The bromine color was discharged almost instantly and copious fumes of hydrogen bromide were evolved. The solution was cooled to room temperature, diluted with an equal volume of carbon tetrachloride, and successively washed with ice-cold water, 1% sodium bisulfite, 1% sodium bicarbonate, and water, and finally dried (Nuchar).

The solution was taken to dryness affording 7.04 g. (100% crude yield) of 1-methyl-2-carboxyethyl-7-bromonaphthalene (**9a** Br) as a yellow-white solid. One recrystallization from 40 ml. of *n*-hexane afforded 4.27 g. (61% yield) of the compound as white prisms, m.p. 75–79.5°.

Further recrystallizations from *n*-hexane and from *n*-hexane–benzene–methanol afforded samples which were submitted for analysis: sample A, m.p. 78–79°, and sample B (duplicate determination), m.p. 78–79.5°. Infrared absorption (CCl_4) showed a peak at 580 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 234.5 (log ϵ 4.69), 275 (3.76), 284.5 (3.77), and 295 mμ (3.57).

Anal. Calcd. for $C_{14}H_{13}O_2Br$: C, 57.36; H, 4.47; Br, 27.26. Found: C, 57.88, 57.25, 57.48; H, 4.47, 4.15, 4.48; Br, 28.54, 27.88, 29.35.

1-Methyl-2-hydroxymethyl-7-bromonaphthalene (**10 Br**) ***via* the Methyl Ester** (**9 Br**).—To a solution of 100 mg. (2.63 mmoles) of lithium aluminum hydride in 20 ml. of dry tetrahydrofuran which had been refluxed for 15 min. was added dropwise over a period of 5 min. a solution of 1.251 g. (4.48 mmoles) of 1-methyl-2-carbomethoxy-7-bromonaphthalene (**9** Br) in 10 ml. of dry tetrahydrofuran. The mixture was refluxed for 1.5 hr., cooled to room temperature, and treated with 1 ml. of ethyl acetate and then 1 ml. of methanol (no visible gas evolution). A few pieces of ice were added, followed by 5 ml. of 1:1 hydrochloric acid. The clear solution was then treated with 5 ml. of saturated sodium chloride solution, the layers were separated, and the aqueous portion was extracted with ether. The combined organic portion was successively washed with water, 2.5% sodium bicarbonate solution, water, and saturated sodium chloride, and dried (Nuchar). The filtered ether solution was taken to dryness *in vacuo* affording 1.04 g. (93% crude yield) of 1-methyl-2-hydroxymethyl-7-bromonaphthalene (**10** Br) as a white solid, which gave 0.817 g. (73% yield) of the compound, m.p. 110–110.5°, softening at 82.5°, after recrystallization from 1:1 benzene–*n*-hexane.

Further recrystallization from *n*-hexane–benzene and from 60:6:1 *n*-hexane–benzene–methanol afforded a sample which was submitted for analysis: m.p. 110.5–111°; infrared absorption (CCl_4), 2.77 μ (—OH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 235.5 (log ϵ 4.91) and broad 285 mμ (3.72); n.m.r., C_1–CH_3, τ 7.48 (singlet), C_2–CH_2–OH, τ 5.24 (singlet), –C_2–CH_2–O*H*, τ 7.87 (singlet), Ar–C_8–H, τ 1.90 (singlet) and other Ar-H at τ 2.22–2.76 (complex multiplet, maximum at τ 2.48).

Anal. Calcd. for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42; Br, 31.82. Found: C, 57.40; H, 4.86; Br, 31.82.

1-Methyl-2-hydroxymethyl-7-bromonaphthalene (**10 Br**) ***via* the Ethyl Ester** (**9a Br**).—To a solution of 300 mg. (7.89 mmoles) of lithium aluminum hydride in 35 ml. of tetrahydrofuran, which had been refluxed for 15 min., was added portionwise (*ca.* 2 ml./min.) a solution of 2.93 g. (10.0 mmoles) of 1-methyl-2-carboxyethyl-7-bromonaphthalene (**9a** Br) in 25 ml. of dry tetrahydrofuran. The mixture was refluxed for 1 hr., cooled to room temperature, and isolated as before.

The crude alcohol (2.10 g., 84% yield—represents minimum, some lost by spillage) was recrystallized from 30:7:3 *n*-hexane–benzene–methanol, affording white crystals, m.p. 110–111°, m.m.p. 110–110.5° with alcohol (m.p. 110.5–111°) from methyl ester procedure. The infrared spectra were identical.

1-Methyl-2-bromomethyl-7-bromonaphthalene (**11 Br**).—To a warm solution of 581 mg. (2.31 mmoles) of 1-methyl-2-hydroxymethyl-7-bromonaphthalene (**10** Br) in 10 ml. of dry carbon tetrachloride was added a solution of 600 mg. (2.22 mmoles) of phosphorus tribromide in 10 ml. of dry carbon tetrachloride. The cloudy mixture was refluxed for 1 hr. and allowed to stand at room temperature for 24 hr.; the solution was decanted from the yellow semisolid (H_3PO_3), which was washed with a little fresh cold carbon tetrachloride. The combined organic portion was washed with water, dried, and taken to dryness *in vacuo* affording 0.607 mg. (94% crude yield) of 1-methyl-2-bromomethyl-7-bromonaphthalene (**11** Br) as a light yellow solid, m.p. 87–91° after two recrystallizations from chloroform–*n*-hexane (charcoal). Further recrystallizations from *n*-hexane afforded a white sample [m.p. 92–93°, ultraviolet peaks at $\lambda_{max}^{CH_3OH}$ 242.5 (log ϵ 4.78) and broad 284 mμ (3.76)] which was submitted for analysis.

Anal. Calcd. for $C_{12}H_{10}Br_2$: C, 45.89; H, 3.21; Br, 50.90. Found: C, 46.06; H, 3.00; Br, 50.48.

Tetralone Reactions. β-(*p*-Bromobenzoyl)propionic Acid.—This compound was prepared in 90% yield (average 67%, from several runs) from purified bromobenzene[18] and freshly recrystallized succinic anhydride (acetic anhydride) using slight modifications of the published procedure.[6] Several recrystallizations from water afforded colorless plates, m.p. 146.5–147° (lit.[6] m.p. 148–149°). It is essential that the commercial anhydrous aluminum chloride be fresh and *white* and that the initial reaction mixture be kept stirred at 0–5° during the slow addition of dilute mineral acid, in order to avoid the formation of very stable foams, from which the product can be isolated only with difficulty in poor yields.

γ-(*p*-Bromophenyl)butyric Acid.—Clemmensen reduction of the succinoylation product afforded a 60% yield of the reduced acid as colorless crystals, m.p. 70–70.5° (lit.[6] m.p. 71–72°) after two recrystallizations from ether–petroleum ether. Unlike the published distillation procedure,[3] the isolation used here was a slow crystallization of the crude yellow oil from ether–petroleum ether at 0–5°. Distillation of the initial crude material afforded lower yields of the acid, whose melting point was raised only after at least four recrystallizations.

7-Bromo-1-tetralone (**12**).—Many PPA cyclizations were carried out, starting with the conditions suggested for γ-phenylbutyric acid.[4,5] Only the optimum conditions are described here.

A mixture of 150 g. of PPA and 36.86 g. (0.152 mole) of γ-(*p*-bromophenyl)butyric acid, initially at room temperature, was heated on a steam bath with stirring for 10 min., at which time the temperature had risen to 80°. It was maintained at this temperature for 45 min., becoming rust colored after only 15 min., and then 200 ml. of ice–water was added.

The suspension was treated with ether, the yellow solid dissolved, and the layers were separated. The ether was washed successively with water, 5% sodium hydroxide, water, 3% acetic acid, 5% sodium bicarbonate, and finally with water. The organic layer was dried and evaporated, affording 24.20 g. (85% crude yield) of a light yellow solid. The product was chromatographed on 200 g. of Merck alumina using first benzene–petroleum ether and then benzene for elution. The solid was recrystallized from ether (Norit) affording 18.31 g. (64% yield) of 7-bromo-1-tetralone (**12**): m.p. 77–78.5° (lit.[3] m.p. 76–77°); infrared (CCl_4), 5.87 μ (C=O).

2-Carboxy-7-bromo-1-tetralone (**13**).—Methylmagnesium carbonate was prepared from 35 g. (0.64 mole) of magnesium methoxide and 33.6 g. (0.84 mole) of "bone-dry" carbon dioxide in 500 ml. of DMF (spectroscopic grade) as previously described.[2] Tetralone **12** (11.1 g., 0.049 mole) was added, and the mixture was stirred and heated at 120–130° for 1.5 hr., then cooled to room temperature, and finally treated with ice and ice-hydrochloric acid mixture. The solid was collected, reprecipitated from 5% sodium bicarbonate (which had been extracted with ether), collected, and dried over phosphous pentoxide. The white solid (6.93 g.), m.p. 103.5–108° (with gas evolution, remelts at 74–75°), was obtained in 52% yield; infrared (KBr), 3.5–4.6 (–CO_2H, broad) and 6.21, 6.30, and 6.44 μ (C=C).

Anal. Calcd. for $C_{11}H_9BrO_3$: C, 49.09; H, 3.37. Found: C, 49.25; H, 3.37.

2-Carbomethoxy-7-bromo-1-tetralone (**14**).—Diazomethane was prepared from DuPont EXR-101[19] and the ethereal solution (in excess) was added to a cold ether solution of 2.51 g. (0.093 mole) of acid **13**. After standing at room temperature overnight, the yellow mixture was treated with a few milliliters of water and allowed to stand several hours. The colorless ether solution

(18) The commercial product was washed successively with 5% sodium hydroxide, 5% hydrochloric acid, water, and saturated sodium chloride, dried over anhydrous sodium sulfate, and then distilled.

(19) N,N′-Dinitroso-N,N′-dimethylterephthalamide.

was washed with 5% sodium bicarbonate, dried, and evaporated *in vacuo*. The oil crystallized on standing in an ice bath, affording 0.83 g. (31% yield) of methyl ester **14**. Recrystallization from petroleum ether afforded colorless crystals: m.p. 49–50° (raised to 52–53.5° by repeated crystallization); infrared (CCl_4), 5.69, 5.87, and a doublet at 6.00 and 6.14 μ. See the corresponding ethyl ester **16** described below.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92; Br, 28.23. Found: C, 51.31; H, 4.43; Br, 26.87.

1-Methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br).—To an ice-cold solution of methylmagnesium iodide, prepared from 1.87 g. (0.078 g.-atom) of magnesium and 14.63 ml. (0.234 mole) of iodomethane in dry tetrahydrofuran (THF), was added a cold solution of keto acid **13** in dry THF. The mixture was stirred for 2 hr. at 0°, allowed to warm to room temperature over a period of 3 hr., and then refluxed for 45 min. The mixture was cooled to 0–3°, decomposed with cold, dilute hydrochloric acid, and the THF was removed by distillation (maximum distillate b.p. *ca.* 100°). The resulting aqueous solution was extracted with ether which in turn was washed with 5% sodium bicarbonate. After acidification of these bicarbonate washings, the acidic products were obtained by extraction with ether which was dried (Norit) and evaporated *in vacuo*. The resulting solid was recrystallized from benzene, affording minute quantities (*ca.* 3–5 mg.) of white needles, m.p. 214.5–215° (evolution of gas).[20]

Ethyl 7-Bromo-1-tetralone-2-glyoxalate (15).—To a cold, fresh solution of sodium ethoxide (prepared from 3.4 g. (0.147 g.-atom) of sodium in *ca.* 30 ml. of dry ethanol) was added over a period of 15 min. with stirring, a warm solution of 24.8 g. (0.110 mole) of 7-bromo-1-tetralone (**12**) and 16.4 g. (0.112 mole) of diethyl oxalate in 30 ml. of dry ethanol. The mixture was stirred in an ice–water bath for 1 hr. and for an additional 6 hr. at room temperature. Cold, dilute sulfuric acid was then added and the mixture was allowed to stand overnight. The dark, tacky solid was collected, dissolved in ether (Norit), dried, and concentrated, affording 26.70 g. (72.5% yield) of oxalyl ester **15** as bright yellow crystals: m.p. 63–65°[21]; infrared (CCl_4), 5.75 (C=O), and 6.11, 6.28, and 6.50 μ (C=C).[22]

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.03; Br, 24.58. Found: C, 51.67; H, 4.15; Br, 24.33.

Ethyl 7-Bromo-1-tetralone-2-carboxylate (16).—The decarbonylation was carried out by heating 25.43 g. (0.078 mole) of oxalyl ester **15** with 2 g. of powdered soft glass at 180–185° at 40 mm. When the vigorous evolution had ceased (*ca.* 30 min.) the pressure was lowered to 0.75 mm. and the fraction distilling at 155–170° was collected, affording 20.35 g. (88% yield) of ethyl 7-bromo-1-tetralone-2-carboxylate (**16**). This was recrystallized from 95% ethanol affording colorless crystals, m.p. 63–66.5°.[23]

Anal. Calcd. for $C_{13}H_{13}O_3Br$: C, 52.54; H, 4.41; Br, 26.89. Found: C, 52.87, 52.62; H, 4.41, 4.71; Br, 27.33, 26.63.

The infrared spectra of **16** (CCl_4) had peaks at 5.77, 5.93, and a doublet at 6.08 and 6.17 μ,. Ethyl 1-tetralone-2-carboxylate is reported also to absorb at 5.77, 5.89, and 6.08 μ, corresponding to the ester carbonyl, the unsaturated keto carbonyl, and the chelated ester, respectively.[24] The methyl ester shows similar absorption (*vide supra*). N.m.r. ($CDCl_3$) showed peaks at τ −2.45 (singlet, enol-OH), τ 2.03 (singlet C_8-H),[25] τ 2.53–3.02 (complex multiplet, Ar-H), τ 5.67 (quartet, $-CO_2CH_2CH_3$), τ 7.32 (unresolved multiplet, may be doublet or triplet, $-CH_2-CH_2-$), and τ 8.63 (triplet, $-CO_2CH_2-CH_3$).

Attempted Preparation of 1-Methyl-2-carbethoxy-7-bromo-3,4-dihydronaphthalene (8b Br).—Methylmagnesium iodide in dry ether was added to a solution of β-keto ester **16** in cold ether. Gas evolution was apparent immediately, and careful work-up in the usual manner afforded 2.28 g. (77% recovery) of starting material. No further attempts were made to effect this conversion.

(20) A sample of this α,β-unsaturated acid prepared by the lengthy independent synthesis above melts at 215–215.5° with *no observable gas evolution*. It is believed that the procedure here affords a compound containing an appreciable amount of the original keto acid.

(21) Attempts were made to prepare the *p*-nitrophenylhydrazine derivative, but elemental analyses could not be reconciled with a reasonable structure for the red solid, m.p. 178–179°. The approximate formulation is $C_{22}H_{18}BrN_3O_5$.

(22) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 142.

(23) This compound crystallized from ether in both rods and plates, but these were shown to be identical by mixture melting point. This appears to be solely a nucleation phenomenon.

(24) L. J. Bellamy and R. F. Brance, *J. Chem. Soc.*, 4487 (1954).

(25) In the n.m.r. spectra of all naphthalene compounds containing a *peri*-hydrogen *ortho* to a halogen atom, we find a distinct separation of this proton from the remainder of the aromatic ones.

The Synthesis of 4-Aminoisoxazolo[5,4-*d*]pyrimidines[1]

EDWARD C. TAYLOR AND EDWARD E. GARCIA

Department of Chemistry, Princeton University, Princeton, New Jersey

Received December 5, 1963

A number of derivatives of isoxazolo[5,4-*d*]pyrimidine have been prepared as potential purine antagonists. Condensation of hydroxylamine with methylethoxymethylenemalononitrile, ethylethoxymethylenemalononitrile, and phenylmethoxymethylenemalononitrile gave a series of 3-substituted 4-cyano-5-aminoisoxazoles which, upon reaction with ethyl orthoformate–acetic anhydride, followed by an amine, gave 4-amino- and substituted aminoisoxazolo[5,4-*d*]pyrimidines. The structures of several of the 4-substituted amino derivatives were confirmed through independent synthesis by heating the 4-amino derivative with a mixture of the alkyl amine and its hydrochloride salt. Catalytic reduction of the 4-aminoisoxazolo[5,4-*d*]pyrimidines resulted in cleavage of the O–N bond; hydrolysis of the resulting imine then gave 4-amino-5-acetyl- and 5-benzoyl-6-hydroxypyrimidines. Several derivatives of the pyrido[2,3-*d*]pyrimidine ring system were prepared by subsequent reaction with malononitrile.

There is continuing interest in the preparation of potential purine antagonists for studies in cancer chemotherapy, since many of the currently active purine derivatives and analogs exhibit excessive toxicity and are unsuited for clinical use. One may cite as an example 4-aminopyrazolo[3,4-*d*]pyrimidine, which, although active as a purine antimetabolite, shows signs of hepatotoxicity in man.[2] Many derivatives of 4-aminopyrazolo[3,4-*d*]pyrimidine (and related purine analogs) have been prepared in an attempt to improve the antitumor activity and reduce the toxicity of the parent compound.[3] We wish to describe in this paper the synthesis and chemical properties of some derivatives of the little-known, structurally related isoxazolo[5,4-*d*]pyrimidine ring system.

The preparation of a bicyclic ring system, such as the desired isoxazolo[5,4-*d*]pyrimidine system, can be approached from either of two directions; that is, the

(1) This work was supported by a research grant (CY-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) R. K. Shaw, R. N. Shulman, J. D. Davidson, D. P. Rall, and E. Frei, *Cancer*, **13**, 482 (1960).

(3) See E. Y. Sutcliffe, K. Y. Zee-Cheng, C. C. Cheng, and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 588 (1962), and preceding papers cited therein.