[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY, AND THE CHEMISTRY DEPARTMENT, TECHNION, ISRAEL INSTITUTE OF TECHNOLOGY]

2,3-Dichloroindone as a Dienophilic Compound

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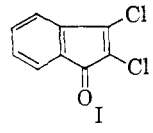
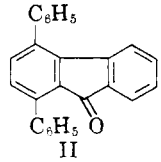
2,3-Dichloroindone reacts with dienes to form fluorenone derivatives. 2-Chloro-3-methylbutadiene gives 3-chloro-2-methylfluorenone. This has been proved by an unambiguous synthesis of the isomeric 2-chloro-3-methylfluorenone. The dipole moments of 3-chloro-2-methylfluorenone and of 2- and 3-bromofluorenone are reported. The reaction between acetylanthranil and Grignard compounds to give *o*-acetaminophenyl ketones and tertiary *o*-acetaminophenylcarbinols has been studied systematically.

One of the modifications of the diene synthesis which leads directly to aromatic (not hydroaromatic) reaction products consists in the application of a dihalogenated dienophilic compound. The dihalogeno-compounds used so far have been dichloromaleic anhydride,[1] dibromomaleic anhydride,[2] halogenated 1,2-[3] and 1,4-naphthoquinones,[4,5] and chloranil.[5,6]

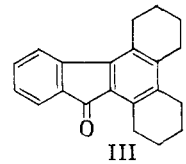
By reaction with dienes, the relatively easily accessible 2,3-dichloroindone (I) permits analogously the synthesis of fluorenone derivatives.



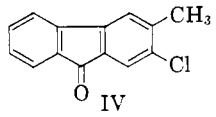
I



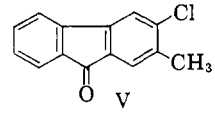
II



III



IV



V

From 1,4-diphenylbutadiene, 1,4-diphenylfluorenone (II) was thus obtained. Dicyclohexenyl gave 1,2,3,4-bis-(tetramethylene)-fluorenone (III).

Comparison of the ultraviolet spectrum of II and III with that of fluorenone[7,8] shows that in both cases a bathochromic shift has taken place (fluorenone, 378; II, 412; III, 394 mμ). While this shift was to be expected in the case of II, one may have to attribute it for III to the same bathochromic effect which a methyl group in the 2-position of the fluorenone system exerts.[7]

By the reaction between I and 2-chloro-3-methylbutadiene (methylchloroprene), a well-crystallized methylchlorofluorenone was obtained for which formulas IV and V are possible. As 2- and 3-methylfluorene are known to form difficultly resolvable mixtures (possibly mixed crystals),[9] the uniformity of the product was proved by the preparation of the semicarbazone which was obtained as a well-defined, homogeneous compound and in practically quantitative yield.

An attempt to decide between formulas IV and V on the basis of the dipole moment (3.14 ± 0.03 D.) failed. From the moments of fluorenone (3.29,[10] 3.35[11]) and 2-bromofluorene (1.68[12]), the moments to be expected for IV and V would be 4.0 and 2.4 D., respectively (the angle between the C—Br and C=O bonds being assumed to be 72 and 132°, respectively). Indeed the moments found for 2-bromofluorenone (3.81 ± 0.04 D.) and 3-bromofluorenone (2.52 ± 0.03 D.) show that there are no large effects of interaction between the carbonyl and the halogen atoms. As has been shown elsewhere,[13] also the moments of 2- and 3-methylfluorenone are only slightly higher than expected from the vectorial addition of the group moments; thus the high moment of the methylchlorofluorenone remains unexplained.

In order to decide between formulas IV and V, an attempt was made to synthesize these compounds in an unambiguous manner. The chlorination of 3-methylfluorenone gave a product different from the compound in question, perhaps 7-chloro-3-methylfluorenone. Therefore, the method proposed by Lothrop and Goodwin[14] was used for the synthesis of IV. The reaction between acetylanthranil (VI) and 3-chloro-4-methylphenylmagnesium bromide gave the acetyl derivative VII of 2-amino-3′-chloro-4′-methylbenzophenone (VIII). The corresponding diazonium salt decomposed, upon heating of its aqueous solution, to give IV. This formula is more likely than the alternative one (IX), in which the cyclization would have involved the position shielded both by the chlorine atom and the carbonyl group.

An attempt to synthesize analogously ketone V from VI and the magnesium derivative of 4-chloro-3-methylbromobenzene failed, since the yield of 2-acetamino-4′-chloro-3′-methylbenzophenone (X) was too small to permit the next step of the syn-

(1) A. M. Clifford and C. E. Gleim, U. S. Patent 2,391,226 (*C. A.*, **40**, 3136 (1946)).

(2) O. Diels and co-workers, *Ann.*, **478**, 137 (1930).

(3) L. F. Fieser and co-workers, THIS JOURNAL, **56**, 2690 (1934); **59**, 1016, 1021, 1024 (1937); **61**, 417 (1939).

(4) L. F. Fieser and J. T. Dunn, *ibid.*, **59**, 1016 (1937).

(5) E. Clar, *Ber.*, **69**, 1686 (1936).

(6) E. Clar, *ibid.*, **64**, 1676 (1931).

(7) E. Bergmann, G. Berthier, Y. Hirshberg, E. Lowenthal, B. Pullman and A. Pullman, *Bull. soc. chim. France*, **18**, 669 (1951).

(8) E. Bergmann, Y. Hirshberg, D. Lavie, Y. Sprinzak and J. Szmuszkovicz, *ibid.*, **19**, 703 (1952).

(9) O. Kruber, *Ber.*, **65**, 1382 (1932).

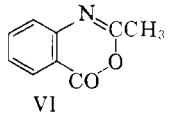
(10) E. Bergmann, L. Engel and H. Hoffman, *Z. physik. Chem.*, **B18**, 159 (1932).

(11) E. D. Hughes, C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 202 (1937).

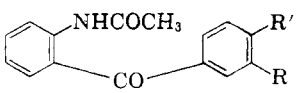
(12) E. Bergmann, G. Berthier, E. Fischer, Y. Hirshberg, D. Lavie, E. Loewenthal and B. Pullman, *Bull. soc. chim. France*, **19**, 78 (1952).

(13) E. Bergmann and E. Fischer, *J. chim. phys.*, **49**, 149 (1942).

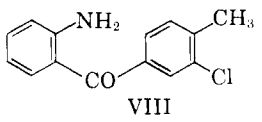
(14) W. C. Lothrop and P. A. Goodwin, THIS JOURNAL, **65**, 363 (1943); *cf.* A. Morrison and T. P. C. Mulholland, *J. Chem. Soc.*, 2302 (1958), and A. Mustafa, *et al.*, THIS JOURNAL, **77**, 1612 (1955).



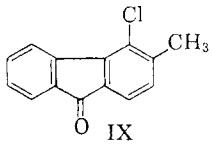
VI



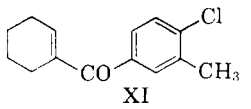
VII, R = Cl, R′ = CH_3
X, R = CH_3, R′ = Cl



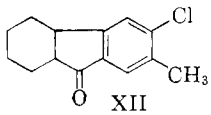
VIII



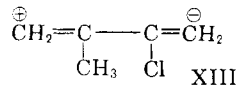
IX



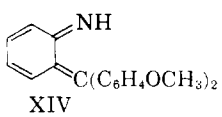
XI



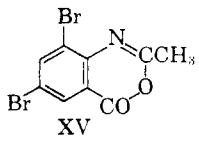
XII



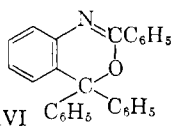
XIII



XIV



XV



XVI

thesis. However, the preceding synthesis of IV gave a product different from that obtained in the condensation of I and methylchloroprene; *per exclusionem*, formula V has thus been proved, if the above argument as to the cyclization of VIII is valid.

This diene condensation, therefore, takes place so that the two most polar groups (the carbonyl and the chlorine atom) in the two reactants reappear in the product at the greatest possible distance from each other, and it can be concluded that methylchloroprene appears to be polarized (XIII) in the same manner as chloroprene,[15] the hyperconjugation with the methyl group being outweighed by the effect of the chlorine atom. The formation of V is analogous to the reaction between chloroprene and acrylic acid, methyl acrylate, acrylonitrile, methyl methacrylate and methacrylonitrile.[16-19]

Some experiments were devoted to an alternative method for the synthesis of V, *viz.*, by cycloisomerization of 1-(4-chloro-3-methylbenzoyl)-cyclohexene (XI) to 3-chloro-2-methyl-4b,5,6,7,8,8a-hexahydrofluorenone (XII)[20-22] and subsequent dehydrogenation with palladium. In the last step, no well-defined product was obtained, probably some of the halogen being lost.

(15) H. Lumbroso, *Bull. soc. chim. France*, **20**, 836 (1953).

(16) (a) A. A. Petrov and N. P. Sopov, *Zhur. Obshchei Khim.*, **17**, 2228 (1947) (*C. A.*, **42**, 4957 (1949)); (b) *Zhur. Obshchei Khim.*, **18**, 1781 (1948) (*C. A.*, **43**, 3373 (1949)).

(17) (a) J. S. Meek and W. B. Trapp, THIS JOURNAL, **74**, 2686 (1952); (b) K. Alder, W. Heimbach and K. Neufang, *Ann.*, **586**, 138 (1954).

(18) J. Doucet and P. Rumpf, *Bull. soc. chim. France*, 610 (1954); J. Gillois-Doucet, *Ann. chim.*, [12] **10**, 497 (1955).

(19) N. P. Sopov, *Zhur. Obshchei Khim.*, **25**, 2082 (1955) (*C. A.*, **50**, 8487 (1956)).

(20) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 2208 (1953).

(21) S. Dev, *Chemistry & Industry*, 1071 (1954).

(22) E. D. Bergmann, *Bull. Res. Council Israel*, **5A**, 150 (1955/6).

In connection with the experiments described in this study, it was thought useful to study the extent to which the reaction between acetylanthranil (VI) and aromatic Grignard reagents[14] leads to *o*-acetaminophenylaryl ketones and *o*-acetaminophenyl-diarylcarbinols, respectively. Lothrop and Goodwin[14] obtained upon addition of acetylanthranil to phenyl-, *o*-tolyl- and α-naphthylmagnesium bromide the tertiary carbinols, in the reverse reaction the ketones. The reactions with *m*-tolyl-, β-naphthyl- and benzylmagnesium halides failed.

The results of the present experiments with acetylanthranil are summarized in Tables III and IV. In the case of benzyl chloride, even the inverse reaction gave only the tertiary alcohol, while with *p*-bromophenylmagnesium bromide the ketone was the main reaction product under both sets of conditions.

An unusual reaction was observed with *p*-methoxyphenylmagnesium bromide, from which a well-crystallized red substance, $C_{21}H_{19}NO_2$, was obtained in 37% yield. As this formula differs from that of the expected *o*-acetaminophenyl-di-(*p*-methoxyphenyl)-carbinol by one molecule of acetic acid, structure XIV of an *o*-quinone-methide derivative[23] is tentatively suggested for the compound. This is supported by the spectrum which shows four maxima (237 mμ (4.48), 259 mμ (4.87), 285 mμ (4.32), 355 mμ (4.03)) and resembles the spectrum of β-naphthoquinones.[24]

From the dibromo-N-acetylanthranil of formula XV and phenylmagnesium bromide, a 60% yield of 2-acetamino-3,5-dibromotriphenylcarbinol was obtained. N-Benzoylanthranil reacted with phenylmagnesium bromide to give 2-benzoylaminotriphenylcarbinol in the form of its anhydride (XVI), while N-chloroacetylanthranil failed to react with the Grignard compound, giving—after the workup—only N-chloroacetylanthranilic acid.

Experimental

For the synthesis of 2,3-dichloroindone (I), crude α,β-dichlorocinnamic acid[25] was mixed with an equal weight of phosphorus pentoxide and distilled *in vacuo;* b.p. 140° (14 mm.), m.p. 89–90°. Under these conditions, both isomers of the acid are cyclized.[26]

1,4-Diphenylfluorenone (II).—A mixture of 5 g. of I and 5 g. of 1,4-diphenylbutadiene reacted at 200° with copious evolution of hydrogen chloride. After 10 hours, the product was fractionated under 2 mm. pressure, and the brown-red fraction distilling at 275–278° triturated with glacial acetic acid and recrystallized from butanol. It melted at 115–116°, yield 6.5 g. (80%); $\lambda_{max}^{dioxane}$ 250 mμ (4.80), 336 mμ (3.64), 388 mμ (3.20), 412 mμ (3.20).

Anal. Calcd. for $C_{25}H_{16}O$: C, 90.4; H, 4.8. Found: C, 90.2; H, 5.0.

1,2,3,4-Bis-(tetramethylene)-fluorenone (III).—A mixture of 5 g. of I and 4 g. of dicyclohexenyl[27] was heated at 160° for 6 hours; hydrogen chloride was evolved. The product crystallized upon trituration with a mixture of acetone and alcohol; yield, almost quantitative. From propyl alcohol one obtained brownish-yellow crystals of m.p. 179–180°, which were chromatographed from carbon tetrachloride solution on activated alumina. Development

(23) *Cf.* H. v. Euler and H. Hasselquist, *Arkiv Kemi*, **6**, 139 (1954).

(24) St. Goldschmidt and F. Graef, *Ber.*, **61**, 1858 (1928); *cf.* S. Nagakura and A. Kuboyama, THIS JOURNAL, **76**, 1003 (1954).

(25) R. Stoermer and P. Heymann, *Ber.*, **46**, 1249 (1913).

(26) E. Bergmann and A. von Christiani, *ibid.*, **63**, 2559 (1930).

(27) E. de Barry Barnett and C. A. Lawrence, *J. Chem. Soc.*, 1104 (1935).

of the chromatogram with carbon tetrachloride gave two narrow zones, deep-brown and slightly reddish-brown, respectively (perhaps dehydrogenation products), and a yellow band which contained practically all the material. This zone was eluted and the product recrystallized from glacial acetic acid; it melted at 183°; $\lambda_{max}^{dioxane}$ 268 mμ (4.76), 296 mμ (3.48), 308 mμ (3.48), 336 mμ (3.50), 354 mμ (3.50), 394 mμ (2.80).

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.5; H, 7.0. Found: C, 87.2; H, 7.0.

3-Chloro-2-methylfluorenone (V).—A mixture of 10 g. of methylchloroprene[28,29] and 10 g. of I was refluxed for 12 hours and the product distilled under 20 mm. pressure. Some hydrogen chloride was evolved during the distillation, and at 225° a fraction, weighing 6 g., was obtained, which solidified immediately. From isopropyl alcohol, the product crystallized in lemon-yellow leaflets of m.p. 146–146.5°; λ_{max}^{EtOH} 231 mμ (4.22), 242 mμ (4.26), 251 mμ (4.36), 260 mμ (4.46), 286 mμ (3.06), 307 mμ (3.18), 325 mμ (3.10), 337 mμ (3.08), 390 mμ (3.43).

Anal. Calcd. for $C_{14}H_9ClO$: C, 73.7; H, 4.0. Found: C, 73.5; H, 4.0.

The semicarbazone crystallized from isopropyl alcohol in clusters of yellowish needles of m.p. 300° dec.; yield quantitative.

Anal. Calcd. for $C_{15}H_{12}ClN_3O$: C, 63.2; H, 4.2; N, 14.7. Found: C, 63.1; H, 4.2; N, 14.8.

Chlorination of 3-Methylfluorenone to 7(?)-Chloro-3-methylfluorenone.—A solution of 2.3 g. of 3-methylfluorenone[7] in 10 ml. of carbon tetrachloride was treated at room temperature with 35 ml. of a carbon tetrachloride solution of chlorine containing 0.0204 g./ml., in the presence of a trace of iron and iodine. After 2 hours, the solution was filtered, washed with water and thiosulfate solution and evaporated *in vacuo*. The residue was dissolved in 50 ml. of heptane, chromatographed on activated alumina and eluted with a heptane–benzene mixture. One recrystallization of the product (1.0 g.) from heptane and two more from alcohol gave yellow needles of m.p. 156°, possibly 7-chloro-3-methylfluorenone. Its mixed m.p. with the product of the condensation of I and methylchloroprene was 144–147°.

Anal. Calcd. for $C_{14}H_9ClO$: Cl, 15.4. Found: Cl, 15.3, 15.5.

Synthesis of 2-Chloro-3-methylfluorenone (IV).—(a) Reduction of 2-chloro-4-nitrotoluene (b.p. 144° (26 mm.), m.p. 64°) with tin and hydrochloric acid or its catalytic hydrogenation in alcohol (palladium as catalyst) afforded in 90% yield **4-amino-2-chlorotoluene**, b.p. 76° (3 mm.).

(b) **3-Chloro-4-methyl-bromobenzene.**[30]—A solution of 23 g. of 4-amino-2-chlorotoluene in 60 ml. of 48% hydrobromic acid was diazotized at 10–20° with a solution of 13.8 g. of sodium nitrite in a little water. The diazonium salt solution was added gradually to a solution of 13.6 g. of cuprous bromide in 14 g. of 48% hydrobromic acid, through which steam was passed. The halogen compound formed was thus removed constantly from the reaction mixture. The steam distillate was made alkaline, and the organic layer separated, washed with concentrated sulfuric acid and water, dried and distilled; yield: 20 g. (60%), b.p. 86° (5 mm.), $n^{25}D$ 1.5862, d^{26}_4 1.5383; *MR* calcd. 43.58, found 43.63.

Anal. Calcd. for C_7H_6BrCl: C, 41.0; H, 3.0. Found: C, 42.0; H, 3.3.

(c) **2-Acetamino-3′-chloro-4′-methylbenzophenone** (VII).—To magnesium turnings (1.5 g.) in ether, activated with a little methyl iodide and iodine, 13.4 g. of 3-chloro-4-methylbromobenzene was added in one portion. When the lively reaction had subsided, it was completed by refluxing the solution for 30 minutes. The product then was cooled to 0°, and 9.7 g. of acetylanthranil (VI)[31] in 125 ml. of benzene was added slowly. The reaction product was kept at room temperature for 12 hours and decomposed with ice and sulfuric acid. The organic layer was separated, washed with 25% sodium hydroxide solution and water and dried, and the solvent evaporated. Thus 2-acetamino-3′-chloro-4′-methylbenzophenone (VII) was obtained, which was triturated with methanol, recrystallized twice from cyclohexane and melted at 102°; yield 9.0 g. (53%).

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.9; H, 5.0. Found: C, 66.3; H, 5.2.

In some runs, recrystallization of the crude ketone from cyclohexane left a small amount of crystals which were recrystallized from glacial acetic acid and melted at 188° dec. Analysis showed that this compound was 2-acetamino-3′,3″-dichloro-4′,4″-dimethyltriphenylcarbinol.

Anal. Calcd. for $C_{23}H_{21}Cl_2NO_2$: C, 66.7; H, 5.1; N, 3.4; Cl, 17.1. Found: C, 66.5; H, 5.1; N, 3.6; Cl, 17.0.

(d) **2-Amino-3′-chloro-4′-methylbenzophenone** (VIII) **Hydrochloride.**—A mixture of 4 g. of 2-acetamino-3′-chloro-4′-methylbenzophenone and 25 ml. of half-saturated alcoholic hydrochloric acid was refluxed for 4 hours; to the cooled solution 200 ml. of ether was added. At 0°, the hydrochloride crystallized in needles. They could be purified by precipitation of their solution in isopropyl alcohol with anhydrous ether; yield 2.5 g. (63%), m.p. 138°.

Anal. Calcd. for $C_{14}H_{14}Cl_2NO$: C, 59.4; H, 5.0; N, 5.0. Found: C, 59.7; H, 4.8; N, 5.0.

(e) **2-Chloro-3-methylfluorenone** (IV).[32]—To a solution of 1.5 g. of the foregoing compound in a mixture of 3 ml. of concd. sulfuric acid and 6 ml. of water, a solution of 0.4 g. of sodium nitrite in 8 ml. of water was added at 0°. The reaction mixture was then heated for 30 minutes at 80° and for the same length of time at 100°. The product was cooled and extracted with ether and the ethereal solution washed with 5% sodium hydroxide solution and water. The ether residue crystallized spontaneously to a yellow-greenish mass, which was triturated with methanol and recrystallized from ethyl alcohol. The compound formed yellow needles of m.p. 119°, yield 1 g. (83%).

Anal. Calcd. for $C_{14}H_9ClO$: C, 73.7; H, 4.0. Found: C, 73.9; H, 4.2.

Attempted Synthesis of 3-Chloro-2-methylfluorenone (V). (a) **2-Chloro-5-nitrotoluene.**—A solution of 170 g. of 2-amino-5-nitrotoluene[33,34] in 750 ml. of concentrated hydrochloric acid was diluted with 100 ml. of water and diazotized at 5° with a solution of 115 g. of sodium nitrite in 300 ml. of water. After one further hour of stirring at 5°, the solution was poured, with efficient agitation, into a solution of 175 g. of cuprous chloride in 500 ml. of concentrated hydrochloric acid, and the reaction mixture heated at 80° for 2 hours, cooled and extracted with benzene. The benzene solution was washed with 10% sodium hydroxide solution, 10% hydrochloric acid and water, dried and distilled. The product boiled at 144–147° (19 mm.) and melted at 44° (lit.[35] 44°, yield 166 g. (87%).

(b) **5-Amino-2-chlorotoluene.**—Catalytic hydrogenation of a solution of 150 g. of the foregoing substance in 300 ml. of ethyl acetate in the presence of 1 g. of 10% palladium–charcoal as catalyst proceeded within 3.5 hours at ordinary temperature and pressure. Distillation gave 92 g. (72%) of the amine, b.p. 85–87° (0.2 mm.), m.p. 81° (lit.[36] 83°.

(c) **5-Bromo-2-chlorotoluene.**—A solution of 90 g. of 5-amino-2-chlorotoluene in 330 ml. of 48% hydrobromic acid and 150 ml. of water was diazotized with 50 g. of sodium nitrite in 200 ml. of water. The solution then was added to 110 g. of cuprous bromide in 140 ml. of 48% hydrobromic acid at 80° and the mixture kept at this temperature for 2 hours. Work-up gave 82 g. (63%) of 5-bromo-2-chlorotoluene, b.p. 127–130° (45 mm.).[30,37]

Anal. Calcd. for C_7H_6ClBr: C, 41.0; H, 3.0. Found: C, 41.3; H, 3.2.

(28) W. H. Carothers and D. D. Coffman, THIS JOURNAL, **54**, 4071 (1932).

(29) E. Bergmann and D. Herrman, *ibid.*, **73**, 4013 (1951).

(30) *Cf.* J. B. Cohen and H. E. Raper, *J. Chem. Soc.*, **85**, 1762 (1904); J. B. Cohen and C. J. Smithells, *ibid.*, **105**, 1907 (1914).

(31) E. Mohr and F. Koehler, *Ber.*, **40**, 997 (1907).

(32) The isomeric structure IX is unlikely, but not excluded.

(33) (a) F. Reverdin and P. Crépieux, *Ber.*, **33**, 2497 (1900); (b) H. J. Page and R. R. Heasman, *J. Chem. Soc.*, **123**, 3235 (1923).

(34) A. M. Berckenheim and R. S. Livshith, *Zhur. Obshchei Khim.*, **6**, 1025 (1936); *C. A.*, **31**, 1778 (1937).

(35) "Beilstein," Vol. V, p. 329; Suppl. Vol. V, p. 163; 2nd Suppl. Vol. V, p. 252.

(36) E. Wroblevsky, *Ann.*, **168**, 147 (1873); J. P. Wibaut, *Rec. trav. chim.*, **32**, 213 (1913).

(37) *Cf.* P. S. Varma and V. Sahay, *J. Indian Chem. Soc.*, **11**, 293 (1934) (*C. A.*, **28**, 5049 (1934)).

(d) **Reaction of 4-Chloro-3-methylphenylmagnesium Bromide with Acetylanthranil.**—To a Grignard solution, prepared as described below from 1.5 g. of magnesium and 13.4 g. of 4-chloro-3-methylbromobenzene, a solution of 9.7 g. of acetylanthranil (VI) in 125 ml. of benzene was added at 0°. After 12 hours at room temperature, the resinous product was decomposed with ice and dilute sulfuric acid and the organic layer washed with sodium carbonate solution and water, dried and evaporated. From the residue separated 3.7 g. of **2-acetamino-4′,4″-dichloro-3′,3″-dimethyltriphenylcarbinol,** which melted after recrystallization from butanol at 179°.

Anal. Calcd. for $C_{23}H_{21}Cl_2NO_2$: C, 66.7; H, 5.1. Found: C, 66.6; H, 5.2.

The liquid part of the reaction product boiled at 225–230° (3 mm.) or 180° (0.1 mm.) and formed a viscous yellow oil, which gave the correct analytical figures for **2-acetamino-4′-chloro-3′-methylbenzophenone (X).** The amount obtained of this ketone was too small to warrant a continuation of the synthesis.

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.9; H, 5.0. Found: C, 66.8; H, 5.3.

The 2,4-dinitrophenylhydrazone crystallized from amyl alcohol or a little nitroethane in rust-brown crystals of m.p. 252–253°.

Anal. Calcd. for $C_{22}H_{18}ClNO_5O_5$: C, 56.5; H, 3.9. Found: C, 56.3; H, 4.0.

4-Chloro-3-methylbenzaldehyde.[38]—A solution of 130 g. of 2,4-dimethylchlorobenzene[39] in 300 ml. of carbon tetrachloride was refluxed for 4 hours with 165 g. of N-bromosuccinimide and a trace of benzoyl peroxide. The filtered solution was concentrated and the remaining **4-chloro-3-methylbenzyl bromide** distilled *in vacuo*. It boiled at 160° (15 mm.), yield 165 g. (81%). The product (160 g.) was heated for 5 minutes with 110 g. of hexamine and 400 ml. of glacial acetic acid and the clear solution diluted with 350 ml. of water and extracted with ether; b.p. 110° (0.5 mm.), yield 50 g. (45%), λ_{max}^{EtOH} 261 mμ (3.58). *Anal.* Calcd. for C_8H_7ClO: C, 62.3; H, 4.6. Found: C, 62.5; H, 4.4.

The 2,4-dinitrophenylhydrazone crystallized from butanol in red crystals of m.p. 224°, $\lambda_{max}^{CHCl_3}$ 382 mμ (4.49).

4-Chloro-3-methylbenzoic Acid.[40]—A solution of 50 g. of the aldehyde in 500 ml. of acetone was oxidized for 3 hours at room temperature and one hour at boiling temperature with a solution of 70 g. of potassium permanganate in a mixture of 300 ml. of acetone and 1 l. of water. The acetone was distilled off, the residue diluted with water and acidified. The acid (35 g., 63%) was recrystallized from nitromethane and melted at 208°.

Anal. Calcd. for $C_8H_7ClO_2$: C, 56.5; H, 4.1. Found: C, 56.6; H, 4.4.

The chloride was obtained from the acid with thionyl chloride; b.p. 105° (3 mm.).

1-(4-Chloro-3-methylbenzoyl)-cyclohexene (XI).—To a solution of 21 g. of 4-chloro-3-methylbenzoyl chloride, 10 g. of cyclohexene and 80 ml. of carbon disulfide, 15 g. of aluminum chloride was added at 0° in 5 portions, with stirring, which was continued at the same temperature for 6 hours. After decomposition of the product with ice and concentrated hydrochloric acid, the solvent was distilled off and the residue refluxed for 3 hours with a solution of 6.3 g. of potassium hydroxide in 25 ml. of ethanol. The ethanol was distilled off and the product diluted with water and isolated by extraction with ether; b.p. 135–140° (0.2 mm.), yield 7.5 g. (20%). The infrared spectrum of the liquid showed three peaks in the carbonyl region: 1650, 1690 and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{15}ClO$: C, 71.8; H, 6.4. Found: C, 71.5; H, 6.5.

The 2,4-dinitrophenylhydrazone was recrystallized from isopropyl alcohol and formed orange-red needles of m.p. 175°, $\lambda_{max}^{CHCl_3}$ 388 mμ (3.75).

Anal. Calcd. for $C_{20}H_{19}ClN_4O_4$: C, 57.9; H, 4.6. Found: C, 57.6; H, 4.5.

3-Chloro-2-methyl-4b,5,6,7,8,8a-hexahydrofluorenone (XII).—A mixture of 7 g. of XI, 9 g. of aluminum chloride and 50 ml. of ethylene chloride was stirred for 1.5 hours at room temperature, for 3 hours at 50° and for 1.5 hours at the boiling temperature of the solvent. Decomposition of the product with ice and hydrochloric acid gave 4 g. (57%) of XII, b.p. 150–153° (1 mm.); λ_{max}^{EtOH} 253 mμ (4.01), shoulder at 320 mμ (3.80); ν_{max}^{liq} 1650, 1690 and 1725 cm.$^{-1}$ (possibly both the preceding and this ketone were mixtures of XI and XII in varying ratios).

Anal. Calcd. for $C_{14}H_{15}ClO$: C, 71.8; H, 6.4. Found: C, 71.5; H, 6.4.

The product gave a well-defined, red **2,4-dinitrophenylhydrazone** from butanol, m.p. 197°, $\lambda_{max}^{CHCl_3}$ 397 mμ (4.54), but the dehydrogenation (with 25% palladium–charcoal at 300°) gave only an oil, which could not be defined properly.

Reaction with N-Acetylanthranil (VI).—For the preparation of the ketones, the general procedure described by Lothrop and Goodwin[14] was applied to N-acetylanthranil[41] (b.p. 143° (11 mm.), m.p. 80–82°). For the preparation of the tertiary carbinols, a benzene solution of acetylanthranil was added to 3 moles of the Grignard reagent. It is essential to wash the ethereal solution of the reaction product, after it has been decomposed with ice and acid, with 25% aqueous sodium hydroxide solution in order to eliminate N-acetylanthranilic acid.

Reaction of Acetylanthranil with *p*-Methoxyphenylmagnesium Bromide.—From 7.2 g. of magnesium, 56.0 g. of *p*-bromoanisole and 18.0 of N-acetylanthranil only a small amount of oily material was obtained by the general procedure. However, from the aqueous acid, used for the decomposition of the reaction product, there precipitated upon standing a resinous material which crystallized when treated with aqueous ammonia. From benzene, beautiful red crystals assumed to have structure XIV, m.p. 268–270° dec., yield 37%, were obtained.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.0; N, 4.4. Found: C, 79.3; H, 6.0; N, 4.4.

Dibromo Derivative XV of N-Acetylanthranil.—3,5-Dibromo-2-aminobenzoic acid was prepared according to Freundler[42] in 65% yield; m.p. 270°. The mixture of 17 g. of the acid and 50 ml. of acetic anhydride was heated at 100° for 3 hours, the liquid evaporated *in vacuo* and the residue recrystallized from cyclohexane. The product so obtained formed yellowish needles, which melted at 159–160° and not at 176°, as indicated by Wheeler and Oates.[43] The product gave correct analytical data; yield 72%.

TABLE I

DIELECTRIC CONSTANTS, REFRACTIVE INDICES AND DENSITIES

$\omega \times 10^5$	$\Delta\epsilon \times 10^4$	$\Delta n \times 10^4$	$\Delta d \times 10^6$
	(A) 2-Bromofluorenone		
148	93		
271	170		
375	236		
465	290		180
1590	..	18	615
	(B) Methylchlorofluorenone		
182	91		
334	168		
461	232		
571	289		
1840	..	24	500
	(C) 3-Bromofluorenone		
177	57		
325	96		
556	168		
865	266	11	330
1910	..	26	739

(38) These experiments were carried out by R. Ikan.

(39) A. Vollrath, *Ann.*, **144**, 261 (1867); O. Jacobsen, *Ber.*, **18**, 1760 (1885).

(40) See ref. 39. The acid has been obtained before by direct oxidation of 2,4-dimethyl-chlorobenzene; the direct method described here gave better yields.

(41) E. Mohr and F. Koehler, *Ber.*, **40**, 997 (1907).

(42) P. Freundler, *Compt. rend.*, **149**, 1137 (1909).

(43) A. S. Wheeler and W. M. Oates, THIS JOURNAL, **32**, 770 (1910); R. Lesser and R. Weiss, *Ber.*, **46**, 3937 (1913).

TABLE II

EMPIRICAL CONSTANTS, MOLECULAR REFRACTIONS AND POLARIZATIONS AND DIPOLE MOMENTS

	$C\alpha_0$	β	$C\gamma n_0^2$	R_D calcd., cc.	R_D obsd., cc.	P_∞, cc.	$P_\infty - 1.05 \times R_D$ obsd., cc.	μ, D.
A	1.201	0.446	0.064	64.7[a]	64.7 ± 0.7	360	292	3.80 ± 0.04
B	0.790	.314	.074	66.4[a]	70 ± 1	276	203	3.14 ± .04
C	0.584	.444	.078	64.7[a]	68.5 ± 0.8	200	128	2.52 ± .03

[a] Calculated from the value for fluorene and fluorenone.[11]

TABLE III

"NORMAL" REACTION BETWEEN ACETYLANTHRANIL AND GRIGNARD COMPOUNDS RMgX (3 MOLES)

R	Formula of the product	M.p. or b.p. (mm.), °C.	Recryst. from	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	$C_{21}H_{19}NO_2$ (carbinol)[a]	190[b]	2-Propanol	40[c]				
o-$CH_3C_6H_4$	$C_{23}H_{23}NO_2$ (carbinol)	155	Benzene[d]	60	80.0	80.0	6.7	6.9
m-$CH_3C_6H_4$	$C_{23}H_{23}NO_2$ (carbinol)	158–160	Benzene–petr. ether	42	80.0	79.6	6.7	7.1
	$C_{16}H_{15}NO_2$ (ketone)	220–230 (3[e])		Small				
p-$CH_3C_6H_4$	$C_{23}H_{23}NO_2$ (carbinol)[f]	163	Cyclohexane	55	80.0	81.0	6.7	6.9
o-$CH_3OC_6H_4$	$C_{23}H_{23}NO_3$ (carbinol)	225–227	2-Propanol	45	73.2	73.3	6.1	6.5
α-$C_{10}H_7$	$C_{29}H_{23}NO_2$ (carbinol)	218[g]	Nitrobenzene; xylene	30	83.5	83.2[h]	5.5	5.5[i]
p-BrC_6H_4	$C_{15}H_{12}NO_2Br$ (ketone)	142[k]	Toluene	25	56.6	56.1	3.8	3.9
$C_6H_5CH_2$	$C_{23}H_{23}NO_2$ (carbinol)	153	2-Propanol	43	80.0	80.0	6.7	6.7

[a] The acetyl-free compound has been described by S. Inagaki, *J. Pharm. Soc. Japan*, **53**, 686 (1933) (*C. A.*, **28**, 2003 (1934)), and by P. Ruggli and B. Hegedues, *Helv. Chim. Acta*, **24**, 703 (1941). [b] *Cf.* A. von Baeyer and V. Villiger, *Ber.*, **37**, 3191 (1904). [c] With two moles of phenylmagnesium bromide the yield was only 30%. [d] From the mother liquor, 2-methyl-4,4-di-*o*-tolyl-3,1,4-benzoxazine (as IV) was isolated by distillation (195–205° (2 mm.)) and recrystallization from methanol; m.p. 160°. (*Anal.* Calcd. for $C_{23}H_{21}NO$: C, 84.4; H, 6.4. Found: C, 84.1; H, 6.4.) The infrared spectrum of the compound shows at 1690 cm.$^{-1}$ the (relatively weak) C=N band. A strong band at 757 cm.$^{-1}$ indicates the *o*-tolyl radicals. [e] 2,4-Dinitrophenylhydrazone, from butanol, m.p. 235°. [f] For the acetyl-free compound see: S. Inagaki, *J. Pharm. Soc. Japan*, **59**, 5 (1939) (*C. A.*, **33**, 3790 (1939)). [g] Literature[25] m.p. 209–210°. [h] The carbinol loses water easily and tends to form the anhydride. [i] Calcd.: N, 3.3. Found: N, 3.2. [k] 2,4-Dinitrophenylhydrazone m.p. 80–82°.

TABLE IV

"INVERSE" REACTION BETWEEN ACETYLANTHRANIL AND GRIGNARD COMPOUNDS RMgX (1 MOLE)

R	Formula of product	M.p. or b.p. (mm.), °C.	Recrystd. from	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
o-$CH_3C_6H_4$	$C_{16}H_{15}NO_2$ (ketone)[a]	102[b]	Petr. ether	28	75.9	76.2	6.0	6.3	5.6	5.4
		180–182 (0.8)								
m-$CH_3C_6H_4$	$C_{16}H_{15}NO_2$ (ketone)	75–76	Cyclohexane	33	75.9	75.5	6.0	6.4	5.6	5.3
		205–210 (2)								
p-$CH_3OC_6H_4$	$C_{16}H_{15}NO_3$ (ketone)[c]	118–119	Benzene–petr.	31	71.4	71.6	5.6	5.8	5.2	5.1
		210–215 (0.5)	ether							
p-BrC_6H_4	$C_{15}H_{12}NO_2Br$ (ketone)[d]	143	Methanol	34	56.6	56.8	3.8	4.1		
		220–225 (0.5)								
2,5-$(CH_3)_2C_6H_3$	$C_{17}H_{17}NO_2$ (ketone)[e]	82	Petr. ether	31	76.4	76.5	6.4	6.5	5.2	5.2
		160 (0.02)								
$C_6H_5CH_2$	$C_{23}H_{23}NO_2$ (carbinol)	153–154	2-Propanol	26	80.0	80.1	6.7	6.7	4.1	4.1

[a] The acetyl-free compound has been described by S. Inagaki, *J. Pharm. Soc. Japan*, **59**, 5 (1939) (*C. A.*, **33**, 3790 (1939)). [b] Literature[22] m.p. 104°. [c] For the acetyl-free compound, see S. Inagaki, Table III, ref. *f*, and F. Ullmann and H. Bleier, *Ber.*, **35**, 4273 (1902). [d] For the acetyl-free compound, see H. F. Miller and G. B. Bachman, THIS JOURNAL, **57**, 2443 (1935). [e] The acetyl-free compound has been described by A. Schaarschmidt and J. Herzenberg, *Ber.*, **53**, 1388 (1920).

Anal. Calcd. for $C_9H_5Br_2NO_2$: C, 33.9; H, 1.6. Found: C, 34.2; H, 1.9.

2-Acetamino-3,5-dibromotriphenylcarbinol.—Phenylmagnesium bromide (from 1.5 g. of magnesium and 9.5 g. of bromobenzene) was treated with a solution of 6.8 g. of XV in 200 ml. of benzene and 100 ml. of ether. Part of the carbinol crystallized spontaneously upon decomposition of the reaction product; from isopropyl alcohol, m.p. 214°, yield 60%.

Anal. Calcd. for $C_{21}H_{17}Br_2NO_2$: C, 53.1; H, 3.6. Found: C, 53.1; H, 3.7.

2,4,4-Triphenyl-3,1,4-benzoxazine (XVI).—From benzoylanthranil (from benzene or ligroin; m.p. 122°)[44] and 3 moles of phenylmagnesium bromide, a reaction product was obtained which after treatment with ice and hydrochloric acid, separated almost quantitatively from the cold ethereal solution. It was triturated with methanol and recrystallized from isopropyl alcohol; m.p. 200–203°, yield 42%.

Anal. Calcd. for $C_{26}H_{19}NO$; C, 86.4; H, 5.3. Found: C, 86.7; H, 5.0.

N-Chloroacetylanthranil.—A solution of 21 g. of anthranilic acid and 34 g. of chloroacetyl chloride (b.p. 108–110°) in 100 ml. of toluene was refluxed for 3 hours. When the solvent was evaporated *in vacuo*, a solid, m.p. 183°, remained which was identified as N-chloroacetylanthranilic acid.[45] The acid was refluxed for 3 hours with an excess of acetic anhydride, the liquid was evaporated *in vacuo* and the residue recrystallized from toluene; m.p. 185–186°, yield 60%.

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.4; H, 3.1. Found: C, 55.0; H, 3.5.

When N-chloroacetylanthranil was treated with 3 moles of phenylmagnesium bromide in the usual manner, only N-chloroacetylanthranilic acid, m.p. 183° (from ethanol), was recovered in almost quantitative yield.

(44) R. Anschütz, O. Schmidt and A. Greiffenberg, *Ber.*, **35**, 3477 (1902).

(45) B. Pawlewski, *ibid.*, **38**, 1683 (1905).

Dipole Moments. **2-Bromofluorenone** (m.p. 148°) was prepared according to Courtot[46] and **3-bromofluorenone** (m.p. 165°) according to Miller and Bachman.[47] The latter procedure was modified as follows: the chloride of 2-(*p*-bromobenzoyl)-benzoic acid was prepared by refluxing 26.5 g. of the acid and 18.5 g. of phosphorus pentachloride in 100 ml. of benzene (until no more hydrogen chloride was evolved) and removing the solvent and the phosphorus oxychloride *in vacuo*. It was then dissolved in 100 ml. of dioxane and treated with dry gaseous ammonia until the exothermic reaction had subsided. The reaction product was poured into water and the solid 2-(*p*-bromobenzoyl)-benzamide (yield 90–95%) collected, washed with water and dried at 100°. It melted at 190°. When 24.5 g. of this amide was added at 10° to a solution, prepared from 15.4 g. of bromine and 14.5 g. of potassium hydroxide in 145 ml. of water, a clear yellow solution resulted. A solution of 20.5 g. of potassium hydroxide in 36 ml. of water was added, and the mass heated at 30°, whereupon 2-amino-4'-bromobenzophenone separated. The temperature then was raised to 80° and the product cooled again. Thus, 16.5 g. of the amine precipitated, and 5 g. of the starting material was recovered by addition of sodium bisulfite to the filtrate; the yield was, therefore, 93%. The amine was purified *via* the hydrochloride and converted further into 3-bromofluorenone, as previously described.[47]

The method used for the determination of the moments, and the meaning of the symbols have been described previously.[48,49] The solvent employed was benzene, the temperature 30°. The data are summarized in Tables I and II.

Acknowledgment.—The dipole measurements have been carried out by Dr. E. Fischer, Weizmann Institute of Science, Rehovoth, Israel, and Mrs. Hannah Weiler-Feilchenfeld of the Chemistry Department, Jerusalem. This study forms part of a thesis submitted by R. Barshai to the Technion, Israel Institute of Technology.

(46) Ch. Courtot, *Ann. chim.*, [10] **14**, 5 (1950).

(47) H. F. Miller and G. B. Bachman, THIS JOURNAL, **57**, 2443 (1935).

(48) E. Bergmann, A. Weizmann and E. Fischer, *ibid.*, **72**, 5009 (1950).

(49) E. Fischer, *J. Chem. Phys.*, **19**, 395 (1951).

JERUSALEM AND HAIFA, ISRAEL

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

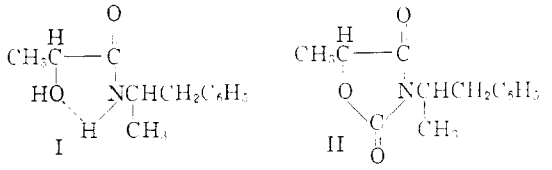
Analeptic Oxazolidinediones and Related Compounds

BY SEYMOUR L. SHAPIRO, IRA M. ROSE, FRANK C. TESTA AND LOUIS FREEDMAN

RECEIVED APRIL 13, 1959

The compound II, 5-methyl-3-(*d*-α-methylphenethyl)-oxazolidine-2,4-dione, has been synthesized and found to have high analeptic activity, comparable to that found with N-(*d*-α-methylphenethyl)-lactamide (I). Thio analogs of I depressed central nervous system activity.

The analeptic activity reported for N-(*d*-α-methylphenethyl)-lactamide (I),[1] indicated exploration of the related oxazolidinedione (II) in which an intact ring replaces the hydrogen-bonded ring proposed for I. Exploration of the scope of structural variation permissive with retention of

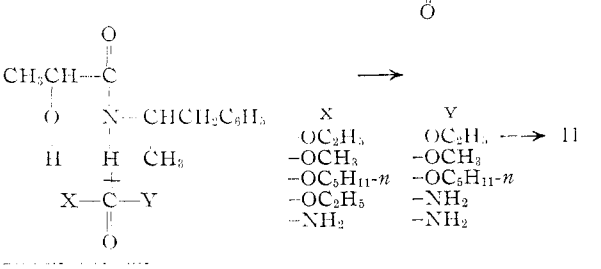


I II

analeptic activity in II also was indicated.[1] The preparation of the carbamate of I was suggested by the reported enhancement of pharmacological activity in hydroxy compounds through introduction of this substituent[2] and the presence of this substituent in effective muscle relaxants (*i.e.*, meprobromate). Additional variants considered were the thio analogs of I and II in view of recent recognition of the improved penetrability of thio analogs into the brain.[3]

For projected synthesis of the dione II, conventional syntheses[4] involving reaction of the acidic hydrogen at the 3-position of the oxazolidinedione ring with a required optically active halide did not appear promising. The halide, α-methylphenethyl chloride, would be difficult to obtain in optically active form and would impose too great a steric factor[5] for effective condensation. The method[6] used was reaction of the *d*,α-methylphenethylamine with ethyl lactate in diethyl carbonate under sodium alkoxide catalysis. The yields of the pure product proved to be low under these conditions, possibly through co-formation of appreciable quantities of the ethyl urethan of *d*-α-methylphenethylamine whose boiling point approximated that of II. Alternative synthesis employing dimethyl carbonate and di-*n*-amyl carbonate which would afford urethans boiling lower and higher than II did not improve the yield.

SCHEME I—VARIATION OF XCY



(1) S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **80**, 6065 (1958).

(2) (a) R. E. McMahon, *ibid.*, **80**, 411 (1958); (b) J. Bauthier and H. Vandersmissen, *Arch. intern. pharmacodyn.*, **119**, 258 (1959); (c) R. Charlier, M. Prost, L. Dierickx, J. M. Ghuysen, M. Urbain and J. Singier, *ibid.*, **119**, 264 (1959).

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(6) S. L. Shapiro, I. M. Rose and L. Freedman, *ibid.*, **81**, 3083 (1959).