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Syntheses of 3,6-Dimethylcholanthrene, 3,6-Dimethyl-7-methoxycholanthrene, and 7-Methoxy-3-methylcholanthrene

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The condensations of 2-lithio-*N,N*-diethyl-1-naphthamide and 2-lithio-*N,N*-diethyl-8-methoxy-1-naphthamide with 4-methyl-1-indanone, followed by hydrolysis, afforded 2-(1-hydroxy-4-methylindan-1-yl)-1-naphthoic acid lactone (**6**) and 2-(1-hydroxy-4-methylindan-1-yl)-8-methoxy-1-napththoic acid lactone (**6a**), respectively. Reduction of **6** followed by esterification yielded methyl 2-(4-methylindan-1-yl)-1-naphthoate (**7a**) which by reaction with methyllithium in ether–hexamethylphosphoramide yielded methyl 2-(4-methylindan-1-yl)-1-naphthyl ketone (**8**). Treatment of **8** with hydrogen fluoride yielded 3,6-dimethylcholanthrene (**1**). Treatment of **8** with 57% hydriodic acid and phosphorus yielded 6,12-dihydro-3,6-dimethylcholanthrene which could readily be oxidized to 3,6-dimethylcholanthrene (**1**). The lactone **6a** was reduced to 2-(4-methylindan-1-yl)-8-methoxy-1-naphthoic acid (**9**). Treatment of **9** with oxalyl chloride followed by reduction with triethylsilane and trifluoroacetic acid yielded a crude product which contained 2-(4-methylindan-1-yl)-8-methoxy-1-naphthaldehyde since it afforded 7-methoxy-3-methylcholanthrene (**3**) on treatment with polyphosphoric acid (PPA). Alternately, methyl 2-(4-methylindan-1-yl)-8-methoxy-1-naphthoate gave 7-methoxy-3-methylcholanthrene on treatment with PPA. Treatment of **9** with 57% hydriodic acid as above gave 8-hydroxy-2-(4-methylindan-1-yl)-1-naphthoic acid lactone (**11**). Treatment of the acid chloride of **9** with dimethylcuprate yielded methyl 2-(4-methylindan-1-yl)-8-methoxy-1-naphthyl ketone (**8a**), which by HF cyclization afforded 3,6-dimethyl-7-methoxycholanthrene (**2**).

The conversion of *o*-lithiated phenyl-4,4-dimethyl-2-oxazolines[2] to substituted benz[*a*]anthracenes[3] has been described. We were interested in applying this general route[4,5] to the synthesis of 3-methylcholanthrenes containing methoxy groups in the angular benzene ring because these could make available phenolic compounds and quinones desired for metabolism studies.[4,6] In this paper the syntheses of 3,6-dimethylcholanthrene[7] (**1**), 3,6-dimethyl-7-methoxycholanthrene (**2**), and 7-methoxy-3-methylcholanthrene (**3**) are described.

The 6-methyl compounds are of particular interest because of the steric factor introduced by the 6-methyl group which should cause molecules containing this feature to be nonplanar just as the 12-methyl group in 7,12-dimethylbenz[*a*]anthracene causes nonplanarity.[8] Since 7,12-DMBA is more carcinogenic than 7-MBA, it was reasoned that 3,6-DMC should be more carcinogenic than 3-MC. [The synthetic work is outlined in Scheme I].

On condensation of the 2-lithium salt of *N,N*-diethyl-1-naphthamide (**5**) with **4** essentially as described[4] a 26% yield of **6** was obtained together with 19% of 2-(4-methyl-1-indenyl)-*N,N*-diethyl-1-naphthamide[9] (**10**) with which no further work has been done. The isolation of this amide together with the enolization of **4** as discussed[4] helps to explain the low yield of **6**. Reduction of **6** afforded **7**, the methyl ester of which, **7a**, was treated with methyllithium to yield the methyl ketone **8**. The formation of a methyl ketone by the reaction of an ester with methyllithium is unusual and is probably due to the high hindrance which causes the first-formed methyl ketone to be tied up as an enolate by the excess methyllithium. Other obvious methods to convert **7** to **8** either failed completely or gave very small yields of **8**. By treatment of **8** with HF a good yield, 49%, of **1** was obtained. Interestingly, treatment of **8** with anhydrous HI in acetic acid and red

(1) Postdoctoral Research Associate supported by the Chemistry Department of the Ohio State University.

(2) Gschwend, H. G.; Hamden, A. *J. Org. Chem.* **1975**, *40*, 2008. Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

(3) Newman, M. S.; Kumar. S. *J. Org. Chem.* **1978**, *43*, 370.

(4) For a similar route with lithiated derivatives of diethylamides[5] applied to the synthesis of 3-methylcholanthrene see: Harvey, R. G.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.* **1982**, *47*, 2120.

(5) Beak, P.; Sniekus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Three workers showed that the diethylamide of 1-naphthoic acid lithiates in the 2-position.

(6) The desirability of syntheses of angular ring-oxygenated methylcholanthrenes for metabolism study aids has been pointed out. For example: King, H. W. S.; Osborne, M. R.; Brookes, P. *Int. J. Cancer* **1977**, *20*, 564. Thakker, D. R.; Levin, W.; Wood, A. W.; Conney, A. H.; Stoming, T. A.; Jerina, D. *J. Am. Chem. Soc.* **1978**, *100*, 645.

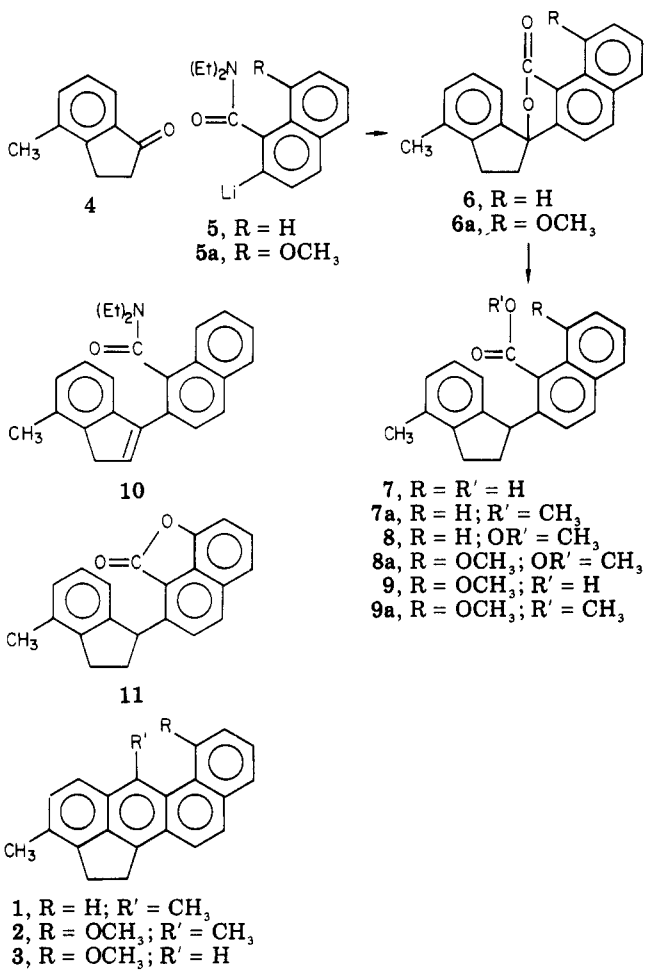
(7) For an alternate synthesis of **1**, see: Newman, M. S.; Sujeeth, P. K. *J. Org. Chem.* **1983**, *48*, 2426.

(8) For the latest X-ray structure and discussion of DMBA see: Jones, D. W.; Sowden, J. M. *Cancer Biochem. Biophys.* **1976**, 281.

(9) The isolation of a small amount of the acid corresponding to this amide was mentioned.[4]

0022-3263/84/1949-2841$01.50/0

Scheme I



P gave a 59% yield of 6,12b-dihydro-3,6-dimethylcholanthrene, which was readily oxidized to **1** by heating with sulfur.[7]

In further development of this route we have found that lithiation of *N,N*-diethyl-8-methoxy-1-napthamide yields the 2-lithio derivative which reacts with **4** to yield **9** in 43% overall yield. All attempts at the reduction of **9** or **9a** with $LiAlH_4$ failed to yield the corresponding alcohol or aldehyde. When refluxing THF was the solvent the ether group was cleaved and a mixture of unknown products was obtained. Attempts to prepare the acid chloride of **9** with $SOCl_2$ or PCl_5 resulted in ether cleavages. However, when **9** was treated with oxalyl chloride in CH_2Cl_2 and the reaction mixture treated with triethylsilane and trifluoroacetic acid, which presumably formed an aldehyde,[10] followed by short treatment with PPA at 100 °C there was obtained a 34% overall yield of **3**. This formation of an aldehyde from an acid chloride is a new reaction as aldehydes are reduced on treatment with triethylsilane in trifluoroacetic acid.[10] An attempt to cause reductive cyclization of **9** with HI failed but yielded 31% of 8-hydroxy-2-(4-methyl-1-indanyl)-1-naphthoic acid lactone (**11**).

When the crude acid chloride of **9** was treated with lithium dimethylcuprate[11] there was obtained 84% of the methyl ketone **8a**, which on cyclization with HF afforded **2** (32%).

Recent biological studies show that 3,6-DMC (**1**) is considerably more carcinogenic than 3-MC.[12,13] This finding supports the concept that noncoplanarity of the benz[*a*]anthracene ring system leads to more potent carcinogenic agents.[14]

Experimental Section[15]

2-(1-Hydroxy-4-methylindan-1-yl)-1-naphthoic Acid Lactone (6). In addition to 0.77 g (26.7%) of **6**, mp 210–211 °C (lit.[4] mp 217 °C), from the reaction[4] of lithio *N,N*-diethyl-1-naphthamide (2.27 g) with 1.40 g of **4**, a 0.66-g (19%) yield of *N,N*-diethyl-2-(4-methyl-1-indenyl)-1-naphthamide (**10**), mp 125–140 °C, was obtained. Although there was a small impurity of *N,N*-diethyl-1-napthamide in this reaction product, the NMR and MS showed that **10** was present in appreciable amount.

2-(4-Methylindan-1-yl)-1-naphthoic Acid (7). Reduction of **6** essentially as described[4] afforded 85% of **7**, mp 211–212 °C and mmp 211–212 °C (with sample of **7** sent by Dr. Harvey) although mp 218–219 °C was reported.[4]

Methyl 2-(4-Methylindan-1-yl)-1-naphthoate* (7a). To a solution formed by stirring 0.2 g of KOH in 1 mL of water and 15 mL of HMPA with 0.604 g of **7** was added 2 mL of methyl iodide. After stirring overnight there was obtained 0.564 g (89%) of **7a**, mp 114–117 °C, suitable for further work. The analytical sample melted at 118–119 °C after crystallization from hexane: NMR (δ) 1.8–3.1 (m, 4, CH_2), 2.3 (s, 3, Ar CH_3), 3.98 (s, 3, OCH_3), 4.5 (t, 1, CH), and 6,6–7.8 (m, 9, Ar H).

Methyl 2-(4-Methylindan-1-yl)-1-naphthyl Ketone* (8). To a solution at room temperature of 0.140 g of **7a** in 10 mL of dry ether was added 1.0 mL of HMPA and 3 mL of 1.4 M methyllithium. After 2.5 h a few milliliters of methanol were added and the product was worked up as usual to yield 0.144 g of colorless gum which afforded 0.071 g of **8**, mp 104–105 °C. A second crop of 0.027 g, mp 102–105 °C (total yield, 74%), was obtained suitable for further work: NMR (δ) 1.8–3.1 (m, 4, CH_2), 2.3 (s, 3, Ar CH_3), 2.6 (s, 3, $COCH_3$), 4.4 (t, 1, CH) and 6.5–7.8 (m, 9, Ar H); MS, *m/e*, 300.0505, calcd for $C_{22}H_{20}O$ 300.0509. Attempts to prepare **8** by reaction of the acid **7** with methyllithium[16] failed completely or gave only traces of ketone.

3,6-Dimethylcholanthrene (1). A solution of 0.100 g of **8** in 6 mL of HF in a polyethylene bottle was allowed to evaporate overnight. After washing with $NaHCO_3$ the product was crystallized from CH_2Cl_2 and chromatographed over Florisil developing with benzene–hexane (1–1). Crystallization from alcohol–methylene chloride yielded 31 mg of **1**, mp 136–137 °C. From the mother liquor and picric acid there was obtained 34 mg of picrate,[7] mp 147.0–148.5 °C. The yield of **1** isolated as **1** and as picrate amounted to 49%.

6,12-Dihydro-3,6-dimethylcholanthrene.[7] A mixture of 27 mg of **8** in 10 mL of acetic acid, 1.7 g of 57% HI, and 0.10 g of

(10) Kursanov, D. N.; Parnes, Z. N.; Loin, N. M. *Synthesis* **1974**, 633.
(11) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**, 4647.

(12) Levin, W.; Wood, A. W.; Chang, R. L.; Newman, M. S.; Thakker, D. R.; Couney, A. H.; Jerina, D. M. *Cancer Lett.* (Shannon, Irel.) *20*, 139. They found that when female CD-1 mice were treated topically with a single dose of compound in 200 μL of 5% DMSO in acetone and ten days later with 16 mmol of 12-*O*-tetradecanoylphorbol-13-acetate in 200 mL of acetone twice weekly for 20 weeks, the mice treated with 3,6-MC got tumors more rapidly and the mice got more tumors than mice treated with 3-MC.

(13) When 16 outbred female rats (Charles River) were injected once subcutaneously at a level of 8 μmol in trioctanoin solution, the rats receiving 3,6-MC had tumors in 4, 12, 14 and 14 animals at 4, 5, 6 and 7 months respectively, whereas with those receiving 3-MC the comparable figures were 0, 5, 10 and 13. This study by J. A. and E. C. Miller, McArdle Laboratory, University of Wisconsin, is continuing.

(14) For an additional example of the nonplanarity effect see the results for 6,8-DMBA and 6,8,12-TMBA: Pataki, J.; Huggins, C. *Cancer Res.* **1969**, *29*, 506.

(15) The term "worked up as usual" means that an ether–benzene solution of the products were washed with dilute HCl, and/or 10% K_2CO_3, and with saturated NaCl and filtered through a cone of anhydrous $MgSO_4$. All new compounds marked by an asterisk gave single spots on TLC analaysis and mass spectra within 5 mmass units of the calculated value (by C. R. Weisenberger on MS9 or DS-55 instruments). NMR spectra were recorded on Varian EM-390 or Brucker HX300 spectrometers with tetramethylsilane as internal standard in $CDCl_3$ unless otherwise specified. All melting points are uncorrected. Methyllithium in ether and *sec*-butyllithium in cyclohexane were obtained from the Aldrich Chemical Co. Elemental analyses by Galbraith Laboratories, Knoxville, TN.

(16) Jorgensen, M. J. *Org. React.* (*N.Y.*) **1970**, *18*, 1.

red phosphorus was refluxed for 1.5 h. After cooling and decolorization with a few drops of 50% hypophosphorous acid there was isolated in the usual way 15 mg (59%) of the dihydro compound,[7] mp 171–173 °C. Recrystallization from acetone–methanol gave 8 mg of colorless product, mp and mmp (with authentic sample[7]) 172.5–173.5 °C.

***N,N*-Diethyl-8-methoxy-1-naphthamide* (5a).** 8-Methoxy-1-naphthoic acid, mp 155–156 °C (lit.[17] mp 159–160 °C), was prepared from 1,8-naphthalic anhydride via the anhydride of 8-(hydroxymercuri)-1-naphthoic acid[18] and 8-iodo-1-naphthoic acid, mp 155–156 °C, by using the procedure previously used for 8-bromo-1-naphthoic acid.[17] The overall yield of 8-methoxy-1-naphthoic acid from 1,8-naphthalic anhydride was 53%. This acid was treated with 1 equiv of PCl_5 in CH_2Cl_2. After all reaction had ceased at reflux the volatile components were removed and a solution of the acid chloride in CH_2Cl_2 was treated with excess diethylamine to yield 92% of **5a**. Purification was most easily accomplished by vacuum distillation which gave a colorless viscous oil, bp 200–203 °C (2.4 mm). Crystallization from hexane yielded **5a**: mp 64–65 °C; NMR δ 0.7–1.3 (m, 6, CH_3), 2.7–3.9 (m, 4, CH_2), 3.7 (s, 3, OCH_3), 6.6–7.7 (m, 6, Ar H); MS, *m/e* 257.1423 calcd for $C_{16}H_{19}NO_2$ 257.1416.

2-(1-Hydroxy-4-methylindan-1-yl)-8-methoxy-1-naphthoic Acid Lactone* (6a). Lithiation of 3.20 g of **5a** in 100 mL of ether essentially as described for *N,N'*-diethyl-1-naphthamide,[4] followed by reaction with 1.818 g of **4**[19] afforded a product which after chromatography over 40 g of neutral alumina with benzene:hexane, 1:1, yielded 1.452 g (35%) of **6a**: colorless needles; mp 127–128 °C; (KBr) 1765 cm^{-1} (C=O); NMR δ 2.4 (s, 3, Ar CH_3), 2.5–3.4 (m, 4, CH_2), 4.1 (s, 3, OCH_3), 6.5–8.1 (m, 8, Ar H); MS, *m/e* 330.1264, calcd for $C_{22}H_{18}O_3$ 330.1255.

2-(4-Methylindan-1-yl)-8-methoxy-1-naphthoic Acid* (9). A mixture of 0.48 g of **6a**, 7 mL of pyridine, 6 mL of methanol, 3.5 g of activated zinc,[20] and 1 g of KOH was refluxed until most of the methanol had distilled. After keeping at reflux overnight the mixture was worked up as usual after filtration of the zinc and acidification to yield 0.45 g of **9** as a white powder, mp 238–240 °C. One crystallization from toluene–hexane yielded 0.43 g (90%) of **9**: mp 239–240 °C; IR 1700 cm^{-1} (C=O); NMR (CD_3COCD_3, $CDCl_3$) δ 2.3 (s, 3, Ar CH_3), 2.2–3.2 (m, 4, CH_2), 3.95 (s, 3, OCH_3), 4.7 (t, 1, CH), 6.7–7.8 (m, 8, Ar H); MS, *m/e* 332.1420, calcd for $C_{22}H_{20}O_3$ 332.1412. When the crude condensation product of **4** and **5a** was submitted to zinc and alkali reduction as described above, a 43% overall yield of **9** was obtained.

7-Methoxy-3-methylcholanthrene* (3). A solution of 55 mg of **9** in 5 mL of CH_2Cl_2 and 1 mL of oxalyl chloride was refluxed for 15 min. The gum obtained on evaporation of the mixture was dissolved in 1 mL of CCl_4 and stirred with 20 mg of triethylsilane in 2 mL of CCl_4 for 15 min. After addition of 100 mg of trifluoroacetic acid in 2 mL of CCl_4 the mixture was stirred for 15 min and evaporated under reduced pressure. The crude product had IR absorption at 1700 cm^{-1} (aldehyde C=O) and no OH band and the NMR showed a singlet at δ 10.8 (aldehyde CH). This product was stirred with 10 g of PPA at 100 °C for 15 min and worked up as usual to give 17 mg (34%) of light yellow needles of **3**, mp 206–207 °C. The analytical sample was obtained after chromatography over neutral alumina with benzene:ethyl acetate, 9:1, elution, and crystallization from alcohol–CH_2Cl_2: mp 207–208 °C; NMR δ 2.37 (s, 3, Ar CH_3), 3.32–3.36 (t, 2, CH_2), 3.62–3.66 (t, 2, CH_2), 4.1 (s, 3, OCH_3), 7.0–7.7 (m, 7, Ar H), 9.92 (s, 1, 6-Ar H); MS, *m/e* 298.1365, calcd for $C_{22}H_{18}O$ 298.1358. Anal. Calcd for $C_{22}H_{18}O$: C, 88.6; H, 6.1. Found:[15] C, 88.4; H, 6.2.

Alternatively, the methyl ester **9a**, prepared from 100 mg of **9**, as described above for **7a**, was stirred with 15 g of PPA at 100 °C for 15 min and worked up as usual to give 18 mg (20% from **9**) of **3**, mp 206–207 °C.

8-Hydroxy-2-(4-methylindan-1-yl)-1-naphthoic Acid Lactone* (11). A solution of 100 mg of **9**, in 10 mL of acetic acid and 1.7 g of 57% HI containing 100 mg of red phosphorus was held at reflux for 72 h. The product obtained after the usual workup was stirred with 6 mL of acetic anhydride and 10 mL of pyridine for 16 h. After pouring into water and the usual workup there was obtained nearly pure **11** which on chromatography over silica gel with benzene as eluant yielded 28 mg (31%) of **11**: mp 165–166 °C; IR (KBr) 1780 cm^{-1} (C=O); NMR δ 2.06–2.30 and 2.4–3.1 (m, 4, CH_2), 2.36 (s, 3, Ar CH_3), 5.56 (t, 1, CH), 6.75–8.03 (m, 8, Ar H); MS, *m/e* 300.1155, calcd for $C_{21}H_{16}O_2$ 300.1150.

Methyl 2-(4-Methylindan-1-yl)-8-methoxy-1-naphthyl Ketone* (8a). A mixture of 0.50 g of **8**, 1 mL of oxalyl chloride, and 3 mL of CH_2Cl_2 was refluxed for 15 min. After removal of volatile matter the product in ether was added to the dimethylcuprate[11] prepared from 0.95 g of Cu_2I_2 and 7.5 mL of 1.4 M methyllithium in ether at room temperature. Water was added after 30 min and the product was chromatographed over 30 g of neutral alumina with benzene–ethyl acetate, 9:1, to yield a crude **8a** which was crystallized from hexane to give 0.415 g (84%) of **8a** as colorless shiny prisms: mp 119–121 °C; IR (KBr) 1700 cm^{-1} (C=O); NMR δ 2.3 (s, 3, Ar CH_3), 2.6 (s, 3, $COCH_3$), 2–3.1 (m, 4, CH_2), 3.9 (s, 3, OCH_3), 4.4 (broad t, 1, CH), 6.6–7.8 (m, 8, Ar H); MS, *m/z* 330.1585, calcd for $C_{23}H_{22}O_2$ 330.1614.

Methyl 2-(4-Methylindan-1-yl)-8-methoxy-1-naphthoate* (9a). From 83 mg of **9** was obtained 80 mg (90%) of **9a**, as described above for **7a**. The ester **9a** was obtained and used as a clear viscous oil: IR (KBr) 1735 cm^{-1} (CO); NMR δ 2.25 (s, 3, Ar CH_3), 1.8–3.2 (m, 4, CH_2), 3.88–3.90 (almost overlapping two singlets, 6, OCH_3), 4.2–4.6 (broad t, 1, CH), 6.7–7.8 (m, 8, Ar H).

On long standing this oil crystallized to give **9a**, mp 132.0–134.0 °C, with the same properties as the oil.

3,6-Dimethyl-7-methoxycholanthrene* (2). In the same way that **8** was converted to **1**, by HF, 50 mg of **8a** yielded 15 mg (32%) of pure **2**, mp 123.0–123.5 °C as fine bright yellow plates; NMR δ 2.48 (s, 3, 3-CH_3), 2.79 (s, 3, 6-CH_3), 3.4–3.8 (m, 4, CH_2), 3.93 (s, 3, OCH_3), 7.0–7.9 (m, 6-Ar H); MS, *m/e* 312.1531, calcd for $C_{23}H_{20}O$ 312.1514. Anal. Calcd for $C_{23}H_{20}O$: C, 88.4, H, 6.5. Found (Galbraith): C, 88.5; H, 6.6.

Registry No. **1**, 85923-37-1; 1 (6,12-dihydro derivative), 90823-02-2; **2**, 90823-08-8; **3**, 90823-04-4; **4**, 24644-78-8; **5**, 78618-70-9; **5a**, 90822-97-2; **6**, 78606-93-6; **6a**, 90822-98-3; **7**, 78606-94-7; **7a**, 90823-00-0; **8**, 90823-01-1; **8a**, 90823-07-7; **9**, 90823-03-3; **9a**, 90823-05-5; **10**, 90822-99-4; **11**, 90823-06-6; 8-methoxy-1-naphthoic acid, 5991-56-0.

(17) Rule, H. G.; Barnett, A. J. G. *J. Chem. Soc.* **1932**, 2728.
(18) Corbellini, A.; Forsati, V. *Chem. Abstr.* **1939**, *33*, 6291.[6]
(19) Synthesized from *o*-tolualdehyde by Dr. V. K. Khanna as described by Young, *Chem. Ber.* **1982**, *25*, 2102.
(20) Activated by stirring for 20 min with 10% HCl, washing with water, grinding with 25% $CuSO_4$ solution (2 mL for 20 g of zinc) being added until the zinc was well covered with water in a mortar.