Tetrahedron. Vol. 29, pp. 3857 to 3859. Pergamon Press 1973. Printed in Great Britain

NEW SYNTHESIS OF 2-SUBSTITUTED RESORCINOLS

N. SCHAMP,* R. VERHE and L. DE BUYCK
Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, State University of Gent, Coupure 533, Gent, Belgium

(*Received in the UK* 1 *July* 1973; *Accepted for publication* 30 *July* 1973)

Abstract—By aromatization of 2-methyl-, 2-benzyl- and 2-acetyl-2-chloro-1,3-cyclohexanedione in dimethylforamide-hydrogen chloride 25%, respectively 2-methyl-, 2-benzyl and 2-acetylresorcinol were obtained in high yields.

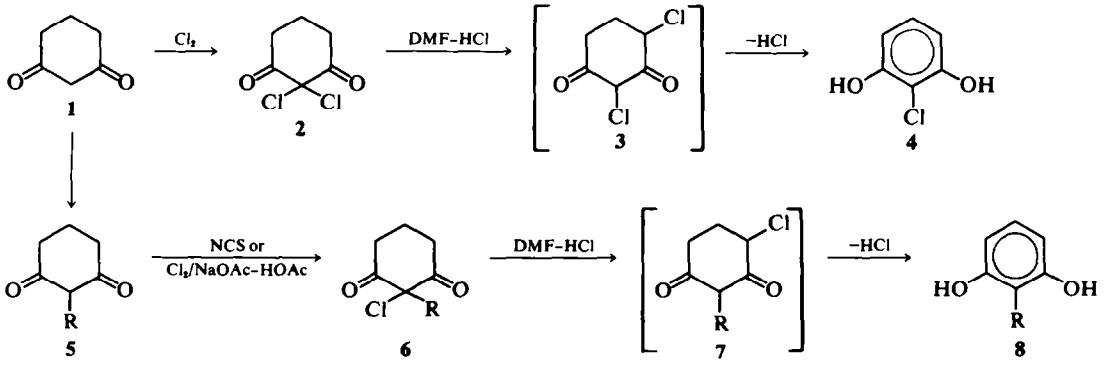
To date syntheses of 2-substituted resorcinols were long and unproductive. The starting materials were 4- and 4,6-substituted resorcinols, especially nitro and carboxyl groups, which can be removed after the substitution at C-2.[1-3] Direct substitution of resorcinol resulted in the formation of both 2- and 4-substitution products except for 2-nitro and 2-lithium derivatives. The reaction of resorcinol with benzylchloride gave a mixture of 4-benzyl-, 2-benzyl-, 2,4-dibenzylresorcinol and small amounts of the mono- and dibenzylether.[4,5] Condensation with allyl-chloride afforded a mixture of 77% 4-allyl-, 4% 2-allyl and 10% 2,4-diallylresorcinol.[6] By the Claisen rearrangement of resorcinol monoallylether, 4-allyl- and 2-allyl-resorcinol were formed.[7]

A number of direct 2-substitutions of olivetol and orcinol with allylic alcohols (*p*-mentha-2,8-dien-1-ol, geraniol, piperitol) have been updated.[8-10] By this method, condensation of resorcinol with linalool and dimethylformamide dineopentylacetal gave 2-(3,7-dimethyl-octa-2,6-dien-1-yl) resorcinol.[11]

Recently a successful synthesis of 2-alkylresorcinols was described by reaction of 2-lithium resorcinol dimethylether with alkyl halides, followed by demethylation.[12] Reaction of the 2-lithium compound of resorcinol bis-tetrahydropyranylether and allylbromide provided 2-allylresorcinol.[13] During an investigation of 1,3-cyclohexanediones a new way to 2-halogen resorcinols was discovered.[14,15] 1,3-Cyclohexanedione (**1**) was chlorinated to 2,2-dichloro-1,3-cyclohexanedione (**2**). The latter was transformed into 2-chloro-resorcinol (**4**) by the reaction with a 25% solution of dry hydrogen chloride in dimethylformamide. In analogy with this reaction, we wish to report the synthesis of 2-methyl-, 2-benzyl- and 2-acetylresorcinol.

2-Methyl-1,3-cyclohexanedione (**5a**) and 2-benzyl-1,3-cyclohexanedione (**5b**) were prepared by treating of 1,3-cyclohexanedione (**1**) with methyliodide and benzylchloride respectively in an alkaline methanol–water solution according to the method of Stetter,[16] while 2-acetyl-1,3-cyclohexanedione (**5c**) was obtained by the reaction of **1** with acetic acid anhydride and sodium acetate.[17]

2-Methyl-1,3-cyclohexanedione (**5a**) and 2-acetyl-1,3-cyclohexanedione (**5c**) were chlorinated



a: R = Me
b: R = $C_6H_5CH_2$
c: R = Ac

Fig 1.

with N-chlorosuccinimide at C-2 in high yields. However the chlorination of **5b** failed. The 2-chloro compound **6b** was synthesized by treatment of **5b** with chlorine in acetic acid/sodium acetate. By the same procedure 2-benzyl-2-bromo-1,3-cyclohexanedione was prepared in excellent yield.

The 2-chloro-1,3-cyclohexanediones **6** were rearranged to 4-chloro-1,3-cyclohexanediones **7** by heating with a 25% solution of dry hydrogen chloride in dimethylformamide.The compounds **7** could not be isolated as aromatization occurred immediately with loss of hydrogen chloride yielding 2-substituted resorcinols (**8**, R = Me, $C_6H_5CH_2$, Ac). This reaction course was proved by the corresponding conversion of 2,2-dichlorodimedone (**9**).[18] In this case 2,4-dichlorodimedone (**10**) could be isolated and was aromatized to 2-chloro-4,5-dimethylresorcinol (**11**) on boiling in 2 N NaOH.

Chlorination of the 1,3-cyclohexanediones **5** (R = Me, $C_6H_5CH_2$) with chlorine in chloroform at 0° gave a mixture of unidentified polychloro 1,3-cyclohexanediones. Aromatization in dimethylformamide-hydrogen chloride of the latter compounds afforded respectively 4,6-dichloro-2-methylresorcinol (**12a**) and 2-benzyl-4,6-dichlororesorcinol (**12b**).

The IR spectra of the 2-substituted 2-chloro-1,3-cyclohexanediones **6** showed the CO band at 1750–1730 cm^{-1}. The NMR spectrum of 2-chloro-2-methyl-1,3-cyclohexanedione (**6a**) exhibited a sharp signal for the Me group at δ 1·57 and a complex multiplet in the region δ 1·2–3·52 for the three methylene functions (A_2B_2CD pattern).

By an approximative first analysis the C-4 and the C-6 methylene functions were calculated, $\delta H_A = 2{\cdot}03$, $\delta H_B = 2{\cdot}69$, $J_{AB} = 1{\cdot}58$, J_{AB} J_{AD} 4·8, $J_{BD} = 6{\cdot}2$, $J_{BC} = 11{\cdot}3$. The spectrum of the C-5 methylene function was too complex to be solved (multiplet δ 1·2–1·6). Direct evidence for the conformation of the Me group was obtained by the treatment developed by Connolly.[19]

The Me function has an equatorial position and the chlorine an axial position based on the slight difference of the chemical shift in benzene and carbon tetrachloride ($\delta_{CCl_4} = 1{\cdot}57$, $\delta_{benzene} = 1{\cdot}61$). The structure of the 2-substituted resorcinols **8** and **12** was confirmed by the IR, NMR and mass spectra. The NMR spectra of **8** showed an AB_2 pattern for the three aromatic protons.

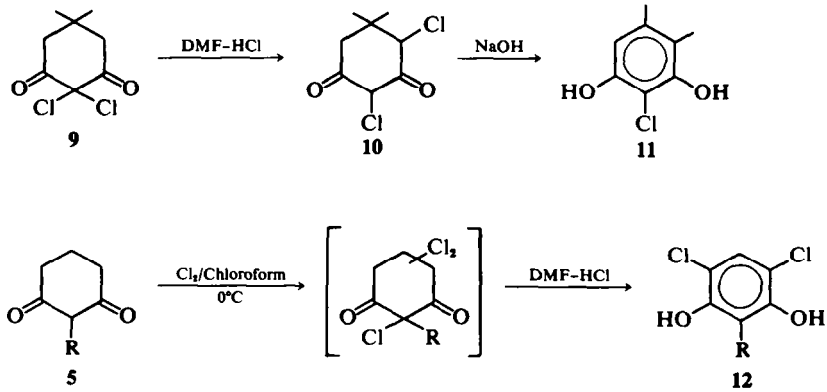
EXPERIMENTAL

I.R. spectra were measured with a Perkin Elmer 257 recording spectrophotometer and the NMR spectra with a Varian A-60 spectrometer, with TMS as an internal standard. Mass spectra were recorded with a AEI MS 30 double beam spectrometer.

2Chloro-2-methyl-1,3-cyclohexanedione (**6a**). A stirred suspension of **5a** (40 g) N-chlorosuccinimide (45 g) in 750 ml dry CCl_4 was refluxed for 15 min. The succinimide was filtered off and the solvent evaporated. Distillation gave 33·5 g of **6a** (65%), b.p. 58°/0·03 mm Hg (deco on standing); ν_{max} (NaCl): 1750–1730 cm^{-1} (CO), δ (CCl_4): 1·57 (3H, s, CH_3); 1·2–3·52 (6H, m, A_2B_2CD, $3 \times CH_2$). (Found: C, 52·4; H, 5·6; Cl, 21·7. Calc. for $C_7H_9ClO_2$: C, 52·3; H, 5·6; Cl, 22·1%).

2-Benzyl-2-chloro-1,3-cyclohexanedione (**6b**). A sat soln of Cl_2 in AcOH (225 ml) was added dropwise to a stirred soln of **5b** (40 g) and anhyd NaOAc (25 g) in 500 ml AcOH at 10°. The soln was stirred for a further 2 h. After trituration with water, the ppt was filtered off, dried and recrystallized from hexane (30 g, 88·5%), m.p. 61°; ν_{max} (KBr): 1740–1720 (CO); 1605, 1500 cm^{-1} (aromatic), δ (CCl_4): 1·19–3·19 (6H, m, A_2B_2CD, $3 \times CH_2$); 3·51 (2H, s, Ar—CH_2—Ar): 7·40 (5H, s, Ar—H). (Found: C, 66·3; H, 5·4; Cl, 14·7. Calc. for $C_{13}H_{13}ClO_2$: C, 66·0; H, 5·5; Cl, 15·0%).

2-Benzyl-2-bromo-1,3-cyclohexanedione. A soln of **5b** (5 g) and NaOAc (3 g) in 200 ml AcOH was treated with a soln of Br_2 in AcOH (8N) until 1·1 equivalent Br_2 has been added. The mixture was poured into 500 ml water. The ppt was recrystallized from hexane (4·97 g, 87·7%) m.p. 64°; ν_{max} (KBr): 1740–1720 (CO); 1605, 1585, 1495 cm^{-1} (aromatic), δ (CCl_4): 1·09–3·07 (6H, m, A_2B_2CD, $3 \times CH_2$); 3·61 (2H, s, Ar—CH_2—Ar); 7·07 (5H, s, Ar—H). (Found: C, 55·4; H, 4·7; Br, 28·3. Calc. for $C_{13}H_{13}BrO_2$: C, 55·5; H, 4·6; Br, 28·4%).



a: R = CH_3
b: R = $C_6H_5CH_2$

Fig 2.

2-Acetyl-2-chloro-1,3-cyclohexanedione (**6c**). A vigorously stirred suspension of **5c** (5·06 g) and N-chlorosuccinimide (4·5 g) in 200 ml dry CCl_4 was refluxed for 4 h. The succinimide was filtered off and distillation gave 4·3 g (69·5%) of **6c**, b.p. 97°/0·03 mm Hg, m.p. 41°; ν_{max} (KBr): 1735–1710 cm^{-1} (CO), δ (CCl_4): 1·75–2·59 (2H, m, CH_2); 2·26 (3H, s, Ac); 2·67–2·91 (4H, m, $2\times CH_2$). (Found: C, 51·0; H, 4·7; Cl, 18·6. Calc. for $C_8H_9ClO_3$: C, 50·8; H, 4·8; Cl, 18·8%).

2-Methylresorcinol (**8a**). A soln of **6a** (16 g) in 150 ml DMF–HCl (25%) was heated at 135° for 15 min under N_2. Rotary evaporation of the DMF left an oil which is hydrolysed by refluxing with 150 ml 6N HCl for 30 min. The mixture was extracted with ether (4×100 ml). The organic layer was washed with a sat $NaHCO_3$ aq and water. The dried extract ($MgSO_4$) was concentrated and crystallization from benzene gave 9·8 g **8a** (79·3%), m.p. 120–121° (Lit.,[20] m.p. 119–121°). ν_{max} (KBr): 3500–3100 (OH); 1610, 1600, 1470 cm^{-1} (aromatic), δ (D_2O): 1·95 (3H, s, Ar—CH_3); 6·26–7·00 (3H, AB_2, $\delta_A = 6·81$, $\delta_B = 6·36$, $J_{AB} = 8·1$ cs, Ar—H); *m/e*: 124(25), 123(11), 107(3), 106(3), 105(3), 95(7), 70(8), 78(100), 77(25), 76(5), 67(5), 63(3), 52(18), 51(20), 50(14).

2-Benzylresorcinol (**8b**). This compound was prepared from **6b** (10 g) and 50 ml DMF–HCl (25%) by the method used for **8a**. Recrystallization from benzene/hexane gave 8·1 g **8b** (79%), m.p. 81° (Lit.,[21] m.p. 82°); ν_{max}(KBr): 3500–3100 (OH); 1610, 1470 (aromatic); δ (dioxane): 4·30 (2H, s, Ar—CH_2—Ar); 5·79–7·05 (3H, m, AB_2, $\delta_A = 6·68$, $\delta_B = 6·10$, $J_{AB} = 8·6$ c/s, Ar—H); 6·95 (5H, s, Ar—H); 7·63 (2H, s broad, OH); *m/e*: 200(99), 199(9), 181(15), 165(4), 154(10), 153(12), 127(8), 123(32), 122(100), 115(5), 94(19), 91(24), 78(14), 77(12), 76(9), 66(8), 65(10), 55(6), 51(12).

2-Acetylresorcinol (**8c**). A soln of **6c** (4·75 g) in 25 ml DMF–HCl (25%) was treated as above. Crystallization from benzene gave 2·9 g **8c** (76%), m.p. 155° (Lit.,[22] m.p. 157°); ν_{max} (KBr): 3500–3100 (OH); 1650 ($COCH_3$); 1595, 1500 cm^{-1} (aromatic); δ (dioxane): 2·65 (3H, s, Ac); 6·01–7·29 (3H, m, AB_2, $\delta_A = 6·95$, $\delta_B = 6·08$, $J_{AB} = 8·0$ cs, Ar—H); 10·70 (1H, s, OH).

4,6-Dichloro-2-methylresorcinol (**12a**). Cl_2 was passed in an ice-cold suspension of **5a** (12·6 g) in 200 ml chloroform during 1 h. Evaporation of the solvent left an oil (15·2 g). Without purification the crude chlorinated **5a** was treated with 150 ml DMF–HCl (25%) by the usual procedure. Distillation and crystallization from ether/isooctane yielded 4·2 g **12a** (37%), b.p. 82°/0·03 mm Hg, m.p. 90–92°; ν_{max} (KBr): 3550–3100 (OH); 1600, 1460 cm^{-1} (aromatic); δ ($CDCl_3$): 2·19 (3H, s, Ar—CH_3); 5·51 (1H, s, broad, OH); 7·11 (1H, s, Ar—H). (Found: C, 43·6; H, 3·2; Cl, 36·8. Calc. for $C_7H_6Cl_2O_2$: C, 43·5; H, 3·1; Cl, 36·8%); *m/e*: 196(11), 195(7), 194(61), 193(17), 192(M^+, 95), 191(16), 160(10), 159 (35), 158(31), 157(100), 129(18), 99(18), 94(15), 73(13), 65(29), 63(16), 53(15).

2-Benzyl-4,6-dichlororesorcinol (**12b**). **5b** (20·2 g) was chlorinated with Cl_2 in chloroform. The crude product was treated with 300 ml DMF–HCl (25%) in the usual way. Crystallization from chloroform/isooctane gave 14·7 g **12b** (54·7%), m.p. 101°; ν_{max} (KBr): 3550–3150 (OH); 1610, 1595, 1495, 1460 cm^{-1} (aromatic); δ ($CDCl_3$): 4·09 (2H, s, Ar—CH_2—r); 5·64 (1H, s broad, OH); 7·28 (6H, m, Ar—H). (Found: C, 58·4; H, 3·8; Cl, 26·3. Calc. for $C_{13}H_{10}Cl_2O_2$: C, 58·0; H, 3·7; Cl, 26·4%); *m/e*: 272(6), 271(5), 270(31), 269(7), 268(M^+,47), 233(5), 194(11), 193(6), 192(60), 191(9), 190(100), 139(7), 115(6), 9(14), 77(8), 75(6), 73(6), 65(11), 63(10), 51(10).

Acknowledgement—The authors thank Prof. M. Verzele (Laboratory of Organic Chemistry—Gent), for performing the microanalyses.

REFERENCES

[1]J. Herzig and E. Wenzel, *Monatsh.* **24** 906 (1903)
[2]R. F. Mulligan and F. S. Hope, *J. Am. Chem. Soc.* **67**, 1507 (1945)
[3]Deshpande, G. R. and S. S. Karamarkar, *Hundustan. Antibiot. Bull.* **9**, 27 (1966)
[4]A. N. Yusupov, *Zh. Khim* (1971); Abstr. Nr. 7zh268
[5]W. J. Hopwood and J. A. Stock, *J. Chem. Soc.* 497 (1965)
[6]I. S. Nikiforova and S. G. Mel'kanovitskaya, *Zh. Organ. Khim.* **72**, 1240 (1966)
[7]K. D. Kaufmann and W. E. Russey, *J. Org. Chem.* **30**, 1320 (1965)
[8]T. Petrzilka, H. Haefliger and C. Sikemeier, *Helv. Chem. Acta* **52**, 1102 (1969)
[9]R. Mechoulam and B. Yagen, *Tetrahedron Letters* 5349 (1969)
[10]B. Cardillo, L. Merlini and S. Servi, *Ibid.* 942 (1972)
[11]Patent France 1, 543, 647; *Chem. Abstr* 72/31435
[12]J. Lille and L. A. Bitter, U. Peinar Festi NSV Tead. *Akad. Toim. Keem. Gcol.* **18**, 365 (1969); *Chem. Abstr.* **72**/121, 114
[13]M. Isob and T. Goto, *Tetrahedron* **24**, 945 (1968)
[14]N. Schamp, *Bull. Soc. Chem. Belges* **73**, 35 (1964)
[15]N. Schamp and H. De Pooter, *Ibid.* **75**, 391 (1966)
[16]H. Stetter, *Neuere Methoden der Präparativen Organischen Chemie*, Band II, 65, Verlag Chemie
[17]H. Smith, *J. Chem. Soc.* 803 (1953)
[18]N. Schamp and M. Verzele, *Bull. Soc. Chim. Belges* **73**, 81 (1964)
[19]J. D. Connolly and R. Mc Grindle, *Chem. & Ind.* 379 (1965)
[20]E. T. Jones and A. Robertson, *J. Chem. Soc.* 1682 (1932)
[21]B. S. Mullaja and R. C. Shah, *Proc. Indian Acad. Sci.* **34A**, 173 (1951)
[22]A. Russel and J. R. Frye, *Org. Synth.* **21**, 22 (1941)