Synthesis and Properties of 5-Bromocyclohepta[*b*]furan-4-one

By **Pierre Crabbé** *† and **Jean-Pierre Deprés**, Laboratoire de Chimie Organique, CERMO, Université Scientifique et Médicale, Grenoble, France

5-Bromocyclohepta[*b*]furan-4-one reacted with ethylamine and isopropylamine to afford the corresponding 6-amino-derivatives by a *cine*-substitution reaction. The behaviour of this compound towards primary amines is different from that of the non-heteroatomic analogue 6-bromobenzocyclohepten-5-one.

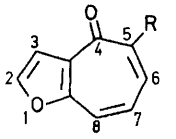
In view of the unexpected behaviour of 6-bromobenzocyclohepten-5-ones with various amines,[1] it was of interest to investigate the chemical reactivity of the corresponding furan analogue (1a) towards amines. The 5-bromo-derivative (1a) was readily prepared from the corresponding furano-suberone (3a).

Condensation of acetaldehyde with furfural (2a) afforded a mixture of conjugated aldehydes (2b) and (2c). Further condensation of (2b) with ethyl acetate gave the conjugated ethyl ester (2d), whereas oxidation of (2c) with manganese dioxide in methanol solution accompanied by esterification provided the corresponding methyl ester (2e). Catalytic hydrogenation of both (2d) and (2e) in the presence of 5% palladium on carbon, followed by alkaline hydrolysis, furnished the same 2-furylpentanoic acid (2f). This was treated with thionyl chloride, followed by reaction with tin(IV) chloride to give the furano-suberone (3a).[2] Optimization of the experimental procedures has allowed the overall yield of the furano-suberone (3a) to be increased substantially.[3] Treatment of the furano-suberone (3a) with methylamine in methanol under pressure afforded the methyl-pyrrolo-suberone (4), dehydrogenation of which with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[4] then gave the *N*-methyl-pyrrolo-tropone (5).

Bromination of the suberone (3a) with trimethyl(phenyl)ammonium tribromide (2 equiv.) gave the dibromo-derivative (3b), which was dehydrobrominated by treatment with lithium carbonate in dimethylformamide to provide the furano-tropone (1b).

Reaction of the dibromo-furano-suberone (3b) with *N*-bromosuccinimide in carbon tetrachloride gave the tribromo-derivative (3c) in high yield. Dehydrobromination of the tribromo-ketone (3c) with lithium carbonate gave the bromo-furano-tropone (1a).

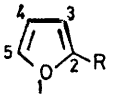
As in the case of 6-bromobenzocyclohepten-5-one,[1] treatment of the bromo-furan analogue (1a) with ethylamine or isopropylamine did not afford any 5-amino-product. Instead, the 6-amino-derivatives (6a) and (6b), repectively, were isolated. Compounds (6a) and (6b) are presumably formed by a mechanism analogous to that in the formation of 7-aminobenzocyclohepten-5-one derivatives.[1] In contrast to the behaviour of 6-bromobenzocyclohepten-5-ones with secondary amines,[1] however, no tricyclic derivative could be isolated. Thus, it appears that the nature of the aromatic unit adjacent to the tropone ring has a direct bearing on the reactivity of the tropone system, in particular in addition processes.



(1)

a; R = Br

b; R = H



(2)

a; R = CHO

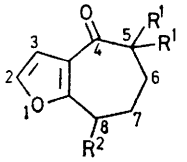
b; R = CH=CHCHO

c; R = [CH=CH]$_2$CHO

d; R = [CH=CH]$_2$CO$_2$Et

e; R = [CH=CH]$_2$CO$_2$Me

f; R = [CH$_2$]$_4$CO$_2$H

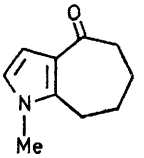


(3)

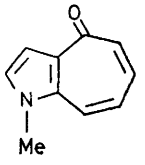
a; R^1 = R^2 = H

b; R^1 = Br; R^2 = H

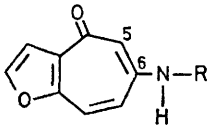
c; R^1 = R^2 = Br



(4)



(5)



(6)

a; R = Et

b; R = Pr^i

EXPERIMENTAL

Microanalyses were performed by the Laboratoire Analytique, C.N.R.S., Lyon. M.p.s were determined with a Büchi Tottoli apparatus. I.r. spectra were recorded for chloroform solutions with a Beckmann Acculab 4 instrument. U.v. absorption spectra were obtained with a Beckmann DBT spectrophotometer. Unless stated otherwise n.m.r. spectra were recorded on a JEOL PMX 60 instrument, for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling

† *Present address*: Department of Chemistry, University of Missouri, Columbia, Missouri 65211.

constants are accurate to ±1 Hz. The mass spectra were obtained with an MS-30 AEI spectrometer. T.l.c. was performed on silica gel plates (Merck 240—400 mesh). We are indebted to Dr. C. Bosso for mass spectral determinations.

Preparation of 5,6,7,8-*Tetrahydrocyclohepta*[b]*furan*-4-*one* (3a).—A mixture of furfural (16 g) and acetaldehyde (40 g) was added slowly to sodium hydroxide (4 g) in water (800 ml), with vigorous stirring.[2] The mixture was then heated at 40 °C for 5 min, neutralized with 2N hydrochloric acid, and extracted with chloroform. After drying, evaporation, and distillation, the aldehyde (2b) (10 g) was isolated at 85—90 °C and 4 mmHg, and the diene-aldehyde (2c) (6.2 g) at 110—115 °C and 4 mmHg. The aldehyde (2b) had m.p. 52 °C; $\lambda_{max.}$ 314 nm (ε 21 000); $\nu_{max.}$ 1 675 and 1 620 cm^{-1}, and the aldehyde (2c) m.p. 62—64 °C; $\lambda_{max.}$ 350 nm (ε 25 000).

To a solution containing powdered sodium (2 g) in ethyl acetate (30 ml) and anhydrous methanol (0.2 ml), kept at −15 °C, the aldehyde (2b) (7.4 g) in ethyl acetate (20 ml) was added with stirring during 2 h.[5] The mixture was stirred for an additional 3 h, then neutralized with aqueous acetic acid, extracted, and chromatographed on silica gel. The ethyl ester (2d) (7 g) was isolated, m.p. 22—23 °C; $\lambda_{max.}$ 337 nm (ε 28 800); $\nu_{max.}$ 1 710 and 1 620 cm^{-1}; δ (CCl_4) 1.22 (t, *J* 9 Hz, CO_2CH_2*Me*), 4.05 (q, *J* 9 Hz, CO_2CH_2Me), and 5.6—7.4 (m, vinylic H).

The aldehyde (2c) (4 g) in methanol (150 ml) was oxidized with manganese dioxide (36 g) and potassium cyanide (5 g) for 12 h at room temperature. After elimination of methanol *in vacuo*, addition of water, and extraction with ether, the product was chromatographed over silica gel, furnishing the methyl ester (2e) (3.7 g) after recrystallization from ethyl acetate–hexane, m.p. 66 °C; $\lambda_{max.}$ 335 nm (ε 30 000); $\nu_{max.}$ 1 710, 1 620, and 1 250 cm^{-1}; δ 3.67 (s, CO_2Me) and 5.7—5.3 (m, vinylic H).

Catalytic hydrogenation of the esters (2d) and (2e) with 5% palladium on carbon in methanol solution under the usual conditions afforded, in 92% yield after purification, the corresponding saturated esters.

Alkaline hydrolysis of these esters with sodium hydroxide in aqueous methanol solution at room temperature, followed by neutralization and extraction with chloroform, provided 2-furylpentanoic acid (2f), which was recrystallized from water, m.p. 42—43 °C; $\nu_{max.}$ 3 060 and 1 710 cm^{-1}.

Treatment of the acid (2f) (13.45 g) with freshly distilled thionyl chloride in anhydrous ether at reflux temperature followed by distillation gave the acid chloride, as a liquid (9.83 g), $\nu_{max.}$ 2 950 and 1 800 cm^{-1}, which was immediately used for the cyclization.

The foregoing acid chloride (2.2 g) in carbon disulphide (7 ml) and tin(IV) chloride (1.7 ml) in carbon disulphide (7 ml) were added simultaneously with stirring to anhydrous carbon disulphide (85 ml) during *ca.* 30 min. The mixture was then gently refluxed, with stirring, for 1 h. Ice was added and the solution concentrated *in vacuo*. Extraction with ether and the usual work-up followed by chromatography over silica gel provided 5,6,7,8-tetrahydrocyclohepta[*b*]furan-4-one (3a) (1.7 g), m.p. 44 °C,[3] $\lambda_{max.}$ 206 (ε 13 000), 216 (sh.), and 266 nm (ε 5 300); $\nu_{max.}$ 1 660 cm^{-1}; δ (CCl_4) 1.95 (m, 6- and 7-H_2), 2.56 (t, *J* 5 Hz, 5-H_2), 2.94 (t, *J* 6 Hz, 8-H_2), 6.54 (d, *J* 2 Hz, 3-H), and 7.14 (d, *J* 2 Hz, 2-H).

Preparation of the 5,5-*Bromo-derivative* (3b).—A solution of trimethyl(phenyl)ammonium bromide (PTT; 2 equiv., 24.5 g) in tetrahydrofuran (THF; 60 ml) was added during 30 min to a stirred solution of compound (3a) (4.9 g) in THF (90 ml) under nitrogen. The mixture was kept for 6 h at room temperature. The usual extraction procedures and recrystallization from methanol gave the dibromo-derivative (3b) (8.1 g), m.p. 110—111 °C;[5] $\lambda_{max.}$ 228 (sh.) and 290 nm (ε 4 400); $\nu_{max.}$ 1 670 and 1 590 cm^{-1}; δ 2.0—2.4 (m, 7-H_2), 3.08 (m, 6- and 8-H_2), 6.77 (d, *J* 2 Hz, 3-H), and 7.3 (d, *J* 2 Hz, 2-H).

Reaction of compound (3a) under the foregoing conditions with 1 equiv. of PTT gave the monobromo-derivative (60%). Recrystallization from methanol furnished pure 5-*bromo*-5,6,7,8-*tetrahydrocyclohepta*[b]*furan*-4-*one*, m.p. 69—70 °C; $\lambda_{max.}$ 282 nm (ε 4 300); $\nu_{max.}$ 1 660 and 1 590 cm^{-1}; δ 2.2—2.5 (m, 6- and 7-H_2), 2.9—3.2 (m, 8-H_2), 4.75 (t, *J* 4 Hz, 5-H), 6.67 (d, *J* 2 Hz, 3-H), and 7.24 (d, *J* 2 Hz, 2-H); *m/e* 228 (M^+) and 200 (M^+ − CO) (Found: C, 47.5; H, 3.9; Br, 34.8. $C_9H_9BrO_2$ requires C, 47.2; H, 3.9; Br, 34.9%).

Preparation of the Tribromo-derivative (3c).—A solution of the dibromo-derivative (3b) (8 g), *N*-bromosuccinimide (4.7 g, 1 equiv.) and benzoyl peroxide (0.1 g) in anhydrous carbon tetrachloride (100 ml), under nitrogen, was heated gently under reflux for 45 min. After cooling, filtration, elimination of solvent, and chromatography, followed by recrystallization from hexane, the tribromo-derivative (3c) (9.5 g) was obtained, m.p. 70—71 °C; $\lambda_{max.}$ 228 (ε 10 200) and 295 nm (ε 5 600); $\nu_{max.}$ 1 685 cm^{-1}; δ 2.4—3.0 (m, 7-H_2), 3.28 (td, J_t 7.5 Hz, J_d 3 Hz, 6-H_2), 5.52 (t, *J* 4 Hz, 8-H), 6.83 (d, *J* 2 Hz, 3-H), and 7.43 (d, *J* 2 Hz, 2-H); *m/e* 384 (M^+), 305 (M^+ − Br), and 277 (M^+ − Br − CO).

Preparation of Cyclohepta[b]*furan*-4-*one* (1a).—Reaction of the dibromo-derivative (3b) (1 g) with lithium carbonate (0.5 g) in anhydrous dimethylformamide (DMF; 17 ml) at reflux for 3 h, followed by the usual isolation and purification procedures gave the cycloheptafuran (1a) (0.32 g), m.p. 44—45 °C;[5] $\lambda_{max.}$ 220 (ε 26 100), 260 (ε 7 200), 300 (ε 7 600), 312 (ε 8 500), 342 (ε 8 800), and 356 nm (ε 8 500); δ 6.6—7.6 (m, 6-H), 7.02 (d, *J* 2 Hz, 3-H), and 7.58 (d, $J_{2,3}$ 2 Hz, 2-H).

Conversion of Compound (3a) *into the Pyrrolo-derivative* (4).—A solution of compound (3a) (2.5 g) in methylamine–methanol (8 ml; *ca.* 50 : 50) and anhydrous methanol (4 ml) was heated at 90 °C in an autoclave for 6 h, then at 130 °C for 40 h.[6] After cooling and evaporation, the crude product was chromatographed on silica gel, to afford 1-*methyl*-5,6,7,8-*tetrahydrocyclohepta*[b]*pyrrole* (4) (2.39 g), which was recrystallized from benzene–hexane, m.p. 60—61 °C; $\lambda_{max.}$ 212 (ε 10 000), 257 (ε 9 700), and 276 nm (sh.); $\nu_{max.}$ 1 640 and 1 510 cm^{-1}; δ (CCl_4) 1.6—2.1 (m, 6- and 7-H_2), 2.3—2.6 (m, 8-H_2), 2.6—2.9 (m, 5-H_2), 3.43 (s, NMe), and 6.22 (2 H, s, 2- and 3-H); *m/e* 163 (M^+) and 134 (M^+ − NMe) (Found: C, 73.5; H, 8.1; N, 8.5. $C_{10}H_{13}NO$ requires C, 73.6; H, 8.0; N, 8.6%).

Preparation of the Unsaturated Derivative (5).—A solution of compound (4) (410 mg), 2,3-dichloro-5,6-dicyanobenzoquinone (3 equiv., 1.7 g) and a few crystals of toluene-*p*-sulphonic acid in anhydrous benzene (25 ml) was heated at reflux temperature for 1.5 h. After cooling and neutralization, the product was extracted with chloroform and purified by t.l.c. to provide the slightly yellow crystalline 1-*methylcyclohepta*[b]*pyrrol*-4-*one* (5) (158 mg), m.p. 72—74 °C; $\lambda_{max.}$ 239 (ε 30 200), 247 (ε 29 900), 312 (ε 10 600), 373 (ε 9 200), and 390 nm (sh.); $\nu_{max.}$ 1 625 and 1 570 cm^{-1}; δ 3.85 (s, NMe), 6.5—7.0 (m, 7-H), 7.0—7.2 (m, 2-, 3-, 5-, and 6-H), and 7.34 (d, *J* 11 Hz, 8-H); *m/e* 159 (M^+), 130 (M^+ − NMe), and 131 (M^+ − CO) (Found: C, 75.6; H, 5.35; N, 8.7. $C_{10}H_9NO$ requires C, 75.45; H, 5.7; N, 8.8%).

Dehydrobromination of the Tribromo-derivative (3c) *to 5-Bromocyclohepta*[b]*furan-4-one* (1a).—A mixture of compound (3c) (9.5 g) and lithium carbonate (3.6 g) in DMF (180 ml) was heated under nitrogen at reflux for 15 min.[5] After cooling, filtration, and elimination of solvent *in vacuo*, the crude product was chromatographed to give the yellow *bromo-ketone* (1a), m.p. 111—112 °C (from C_6H_{12}); $\lambda_{max.}$ 228 (ε 12 400), 257 (ε 14 000), 322 (ε 6 050), 352 (ε 8 700), and 368 nm (ε 9 000); $\nu_{max.}$ 1 620 and 1 600 cm^{-1}; δ 6.5—6.96 (q, 7-H), 7.25 (d, *J* 2 Hz, 3-H), 7.57 (d, *J* 11 Hz, 8-H), 7.73 (d, *J* 2 Hz, 2-H), and 8.16 (d, *J* 9.5 Hz, 6-H); *m/e* 224 (M^+) and 196 (M^+ — CO) (Found: C, 47.8; H, 2.3; Br, 35.6. $C_9H_5BrO_2$ requires C, 48.0; H, 2.2; Br, 35.6%).

Reaction of Compound (1a) *with Ethylamine*.—To ethylamine (50 ml) cooled to −15 °C with acetone–solid carbon dioxide the 5-bromo-derivative (1a) (1.4 g) was added with stirring. The mixture was then kept at −7 °C for 15 h. After removal of ethylamine, the residue was dissolved in ethyl acetate and chromatographed on silica gel. Evaporation and crystallization from methylene chloride–ether gave 6-*ethylaminocyclohepta*[b]*furan-4-one* (6a), m.p. 133—134 °C; $\lambda_{max.}$ 280 (ε 49 000) and 338 nm (ε 6 900); $\nu_{max.}$ 3 450, 1 637, and 1 530 cm^{-1}; δ 1.27 (t, *J* 7 Hz, $NHCH_2\mathit{Me}$), 2.9—3.4 (m, $NHCH_2Me$), 5.9—6.3 (s, NH), 6.10 (d, *J* 2.5 Hz, 5-H), 6.66 (dd, *J* 12 and 2.5 Hz, 7-H), 7.10 (d, *J* 2 Hz, 3-H), 7.18 (d, *J* 12 Hz, 8-H), and 7.53 (d, *J* 2 Hz, 2-H); *m/e* 189 (M^+), 174 (M^+ — Me), and 146 (M^+ — NEt) (Found: C, 69.6; H, 5.8; N, 7.4. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%).

Reaction of Compound (1a) *with Isopropylamine*.—Using a similar procedure to that in the previous section, reaction of compound (1a) (1.5 g) with isopropylamine (80 ml) with stirring for 48 h at −7 °C gave 6-*isopropylaminocyclohepta*[b]*furan-4-one* (6b) (940 mg, 70%), m.p. 130—131 °C (from CH_2Cl_2–C_6H_{12}); $\lambda_{max.}$ 282 (ε 44 000) and 340 nm (ε 7 000); $\nu_{max.}$ 3 440, 1 635, 1 595, and 1 545 cm^{-1}; δ 1.22 (d, *J* 6 Hz, $CH\mathit{Me}_2$), 3.1—3.4 (m, $CH\mathit{Me}_2$), 5.4—5.7 (s, NH), 6.08 (d, *J* 2.5 Hz, 5-H), 6.48 (dd, *J* 12 and 2.5 Hz, 7-H), 7.03 (d, *J* 2 Hz, 3-H), 7.10 (d, *J* 12 Hz, 8-H), and 7.44 (d, *J* 2 Hz, 2-H); *m/e* 203 (M^+), 188 (M^+ — Me), 160 (M^+ — $CHMe_2$), and 146 (M^+ — $NCHMe_2$) (Found: C, 70.8; H, 6.7; N, 7.1. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%).

We thank Dr. R. Gautron for his interest in this work and discussions.

[9/1161 *Received*, 23*rd July*, 1979]

REFERENCES

[1] J. Iriarte, C. Camargo, and P. Crabbé, preceding paper.
[2] R. J. Rolling and J. C. Smith, *J. Chem. Soc.*, 1953, 618.
[3] W. Treibs and W. Heyer, *Chem. Ber.*, 1954, **87**, 1197.
[4] For a review see: D. Walker and J. D. Hiebert, *Chem. Rev.*, 1966, **67**, 153.
[5] See: E. W. Collington and G. Jones, *J. Chem. Soc.* (*C*), 1969, 2656; G. Jones, *ibid.*, 1970, 1230; G. Jones, R. K. Jones, and M. J. Robinson, *J.C.S. Perkin I*, 1973, 968; G. Jones and M. J. Robinson, *ibid.*, 1977, 505, and references therein.
[6] H. Stetter and R. Lauterbach, *Annalen*, 1962, **206**, 665.