# Arynic and SNAr Reactions of Polyhalogenobenzenes. V.[1,2] Synthesis of Benzofurans

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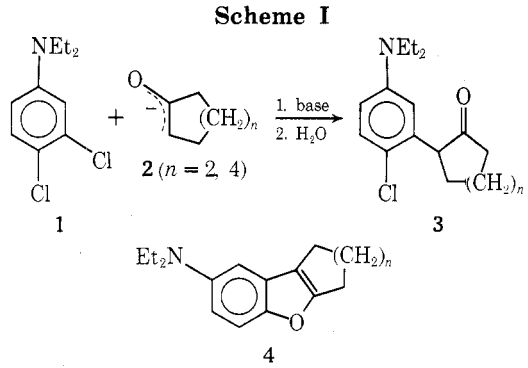
The formation of benzofurans during the condensation of ketone enolates on dialkylamino dichlorobenzenes in the presence of bases in aprotic medium was studied. It was shown that the dialkylamino monochloro phenyl ketones, formed during these condensations, are the intermediates. With suitable experimental conditions the heterocyclic compounds are easily synthesized from dialkylamino dichlorobenzenes in one or two steps. Furthermore, it is demonstrated that this new synthesis of benzofurans is general and applicable to polyhalogenobenzenes starting materials.

In the previous paper, we have observed the formation of small amounts of benzofurans (**4**) in the course of the condensation of cyclohexa- and cyclooctanone enolates with *N,N*-diethylamino-3,4-dichlorobenzene in the presence of bases (Scheme I).

**Scheme I**




In the present work, we study the mode of formation of these heterocycles, and we attempt to make such a reaction suitable for synthesis.

## Results

It seemed reasonable to suppose that **4** originated from **3** under the influence of bases. After having verified this hypothesis by preliminary experiments, we have undertaken the study of these cyclizations. We shall further discuss their mechanism.

**Cyclization of Phenylcyclanone Enolates 5 (Scheme II). Synthesis of 2,3-Polymethylene-5-diethylamino-benzofurans.** We have carried out many systematic runs, varying time, temperature, base, solvent, and dilution. Table I reports only the most interesting results.

From many experiments, carried out in other instances, the following facts can be pointed out.

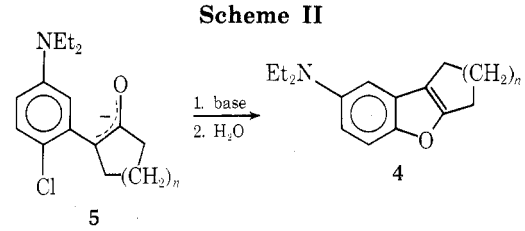
(1) Base and solvent should be properly chosen. In THF, complex base $NaNH_2$–*t*-BuONa[3] should be used. In HMPA–THF, $NaNH_2$ alone should be used; the required quantity of base and reaction time are then markedly decreased. However, for $n = 1$ in HMPA, it is not possible to carry out the cyclization of the arylcyclopentanone, unstable and destroyed in this solvent.[4]

(2) Dilution plays an important part, particularly for $n = 4$. A decrease of dilution, in regard to the values of Table I, generally results in a decrease of the yield, which likely may be attributed to some intermolecular reactions.

(3) Without base, considerable decrease of the yield is observed; thus, in the conditions of run 5, but without sodium amide, no benzofuran is obtained at all.

Practically, Table I shows that compounds **4** are readily accessible from ketones **3**. Taking into account the results of the previous paper, we can consider two pathways for the synthesis of benzofurans (Scheme III).

**Scheme II**




**Scheme III**

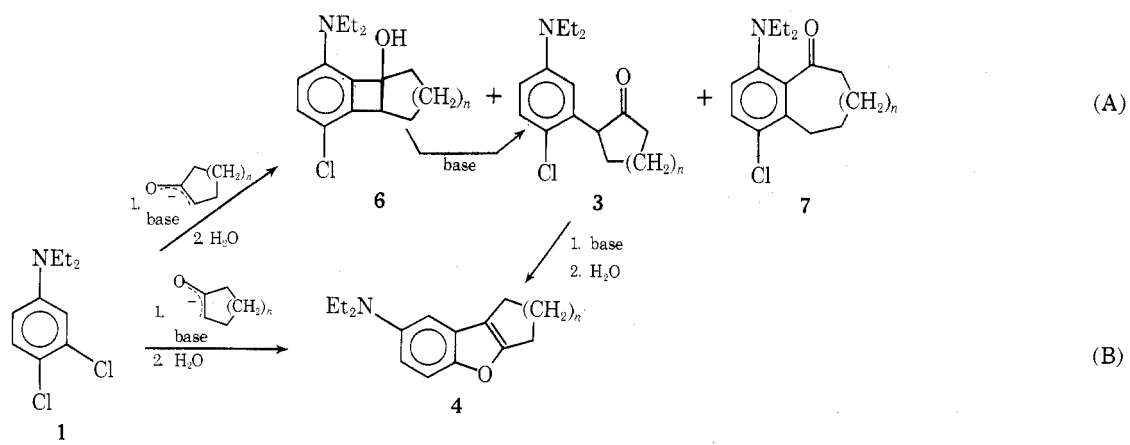


**Table I**
**Cyclization of Enolates 5 into Benzofurans 4 in the Presence of a Base**

| Run | n | 5, mmol | Base (mmol)[a] | Solvent ($cm^3$/mmol of 5) | Temp, °C | Time, hr | 3 recovered, % | 4, % |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 8 | $NaNH_2$-*t*-BuONa (32–16) | THF (13) | 47 | 64 | 4 | 76 |
| 2 | 2 | 9 | $NaNH_2$-*t*-BuONa (27–13.5) | THF (3) | 52 | 16 | 0 | 88 |
| 3 | 2 | 9 | $NaNH_2$ (18) | THF–HMPA 3:1 (8) | 50 | 1.5 | 0 | 79 |
| 4 | 3 | 4.6 | $NaNH_2$-*t*-BuONa (20–10) | THF (13) | 46 | 24 | 3 | 76 |
| 5 | 3 | 7 | $NaNH_2$ (14) | THF–HMPA 3:1 (13) | 65 | 0.75 | 0 | 79 |
| 6 | 4 | 6 | $NaNH_2$-*t*-BuONa (24–12) | THF (13) | 47 | 20 | 5 | 75 |
| 7 | 4 | 7.5 | $NaNH_2$ (15) | THF–HMPA 3:1 (13) | 65 | 2 | 0 | 45 |

[a] The quantity of $NaNH_2$ indicated is the leading sodium amide after formation of tertiobutylate and enolate. (See Experimental Section.)

**Table II**
**Condensation of Enolates 2 (50 mmol) with 1 (18 mmol) in the Presence of Base in 240 ml of Solvent**

| Run | n | Base (mmol) | Solvent | Experimental conditions | 4, %[a] |
|---|---|---|---|---|---|
| 8 | 1 | $NaNH_2$-*t*-BuONa (110–55) | THF | 2 hr at 20° then 48 hr at 50° | 40 |
| 9 | 2 | $NaNH_2$-*t*-BuONa (110–55) | THF | 2 hr at 20-25° then 17 hr at 52° | 48 |
| 10 | 2 | $NaNH_2$ (65) | THF then THF–HMPA 3:1 | 3 hr at 20-25° then 2.5 hr at 50° | 53 |
| 11 | 3 | $NaNH_2$ (65) | THF then THF–HMPA 3:1 | 2 hr at 20-25° then 2.5 hr at 50° | 51 |
| 12 | 4 | $NaNH_2$ (65) | THF then THF–HMPA 3:1 | 50 min at 45-50° then 2.5 hr at 50° | 32 |

[a] Yields of isolated products, calculated with respect to the starting chloro amine.

Route B may be reasonably considered: in basic medium and in a suitable solvent, indeed, alcohols **6** are opened to lead mainly to **3**;[2] and moreover, the formation of **7** may be made very small or totally avoided.[2]

Table II summarizes the essential results of a study carried out with the purpose of realizing, in practice, route B.

It is clear that 5-(*N*,*N*-diethylamino)benzofurans may be directly obtained from the dichloro compound **1**, with quite satisfactory yields. Various runs, not reported here, show that the choice of experimental conditions, and especially of the "base–solvent" system, is important. Thus, for $n = 1$, use of $NaNH_2$ in THF–HMPA mixture led to formation of only traces of benzofurans, whereas for $n = 3$ and 4 this is the only efficient system. On the other hand, for $n = 2$, both media are suitable.

In conclusion, taking into account what we described in the preceding paper, it appears that, as far as yields are concerned, routes A and B are comparable. Route B is preferable since it is carried out in *only one* pot.

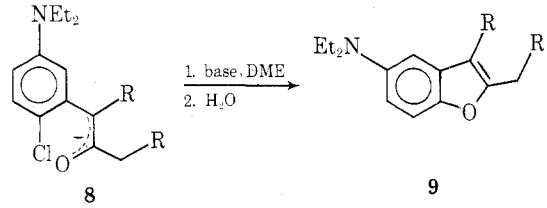
**Cyclization of Phenyl Ketone Enolates 8 (Scheme IV).** Ketones of this type can be prepared by means of the reactions described in the preceding paper. The conditions used for the cyclizations of arylcyclanones are not suitable here, and some preliminary runs led us to use the system $NaNH_2$–*t*-BuONa in DME. The results are summarized in Scheme IV and Table III.

Temperature and amounts of base lower than those mentioned in Table III strongly decrease the yields.

**Table III**
**Cyclization of 8 (10 mmol) in the Presence of $NaNH_2$ (50 mmol)-*t*-BuONa (25 mmol) in DME (130 ml)**

| Run | R | Temp, °C | Time, hr | 8-H recovered, % | 9, % | 9 + 8-H, % |
|---|---|---|---|---|---|---|
| 13 | $CH_3$ | 75 | 20 | 13 | 56 | 69 |
| 14 | *n*-$C_3H_7$ | 80 | 21 | 0 | 55 | 55 |

**Scheme IV**




8 9

On the other hand, attempts at direct cyclization (route B of the preceding section) have been so far unsuccessful.

**Cyclization of Phenyl Ketone Enolates 10.** The starting ketone has no enolizable benzylic hydrogen atom. In basic conditions the formed enolate **10** is cyclized, following the reaction of Scheme V.

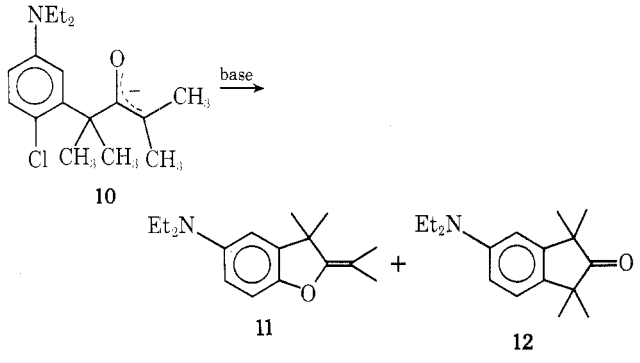
After short systematic studies, we have retained, as interesting for synthesis, the runs reported in Table IV.

Run 16 is satisfactory for the synthesis of **11** and run 15 is a way of formation of the ketone **12**.

**Table IV**
**Cyclization of 10 (7 mmol) in the Presence of a Base in 90 ml of Solvent**

| Run | Base (mmol) | Solvent | Temp, °C | Time, hr | 11, % | 12, % | Total yield, % |
|---|---|---|---|---|---|---|---|
| 15 | $NaNH_2$-*t*-BuONa (28–14) | THF or DME | 50–60 | 21–23 | 65 | 35 | 75–80 |
| 16 | $NaNH_2$ (14) | THF–HMPA 3:1 | 57 | 3 | 82 | 18 | 75 |

**Scheme V**




Attempts at direct syntheses of **11** and **12** from the dichloro derivative **1** were synthetically unsuccessful.

## Discussion

With **13** and **14** being the intermediates corresponding, respectively, to ketones enolizable or not enolizable at the benzylic position, two reaction paths (SNAr or AE) (Scheme VI) may be a priori considered.

We cannot discard the occurrence of some SNAr, particularly in the presence of HMPA, which favors, at the same time, these reactions[5] and O-alkylations of enolates.[6] However, we have seen that in the absence of base, cyclization yields were *strongly decreased*. It seems therefore quite reasonable to think that the arynic mechanism is markedly preponderant.

On the other hand, competition between O- and C-arylations is possible in all cases. When the ketone has a benzylic hydrogen atom, C-arylation would lead to an instable benzocyclopropene, and O-arlyation only is observed. If there is no benzylic hydrogen atom, competition becomes effective, and a mixture of ketone and oxygen heterocycle is obtained. According to what we expected,[6] O-arylation is favored in HMPA (cf. Table IV).

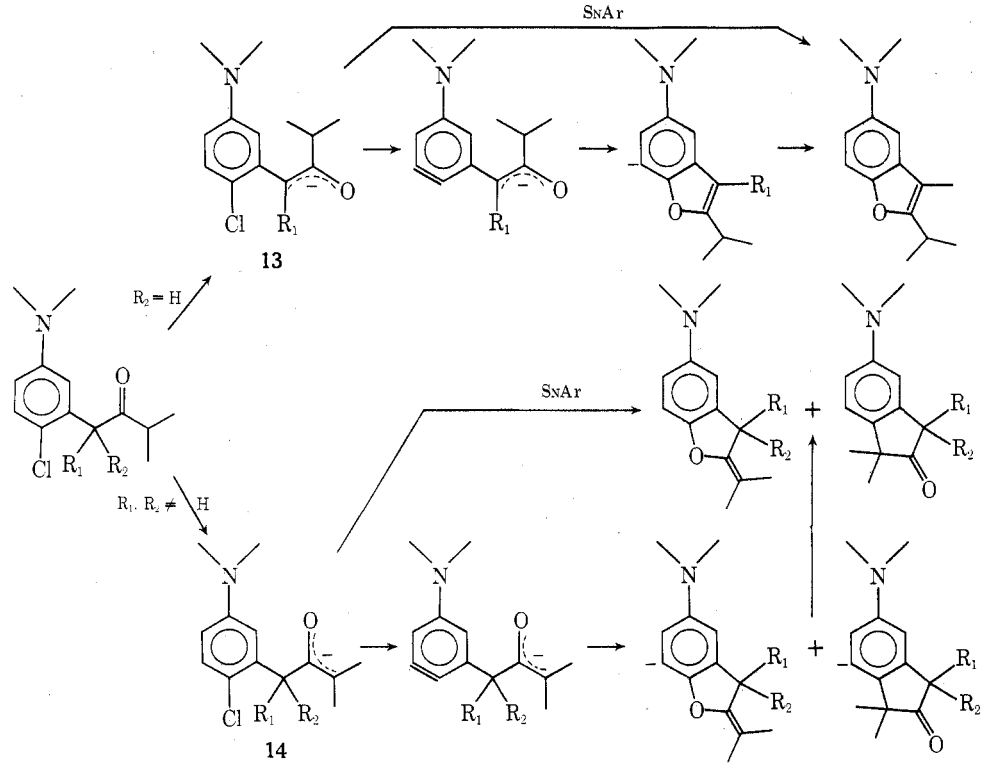
Lastly, we may compare these reactions with arynic heterocyclizations of amides and thioamides, carried out in liquid $NH_3$.[7–9] Curiously, in this solvent, aryl 2-ketones lead to an indolic heterocycle[7,8] rather than to a benzofuran.

**Synthesis of 6-Morpholinobenzofurans.** If the hypothesis about the intervention of an aryne in the formation of benzofurans **4** is true, it should be possible to carry out the synthesis of 6-aminobenzofurans from morpholino-2,3-dichlorobenzene (**15**) (Scheme VII). This chloro derivative has been prepared previously, by condensing morpholine with 1,2,3-trichlorobenzene,[10] and its reactivity is well known.[11]

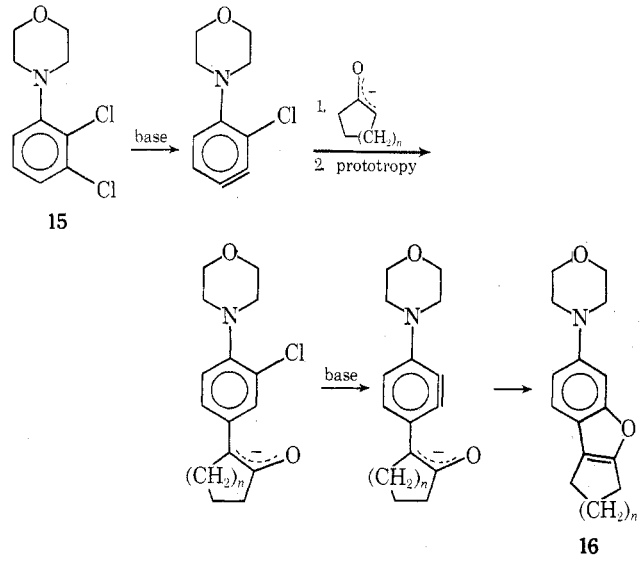
We have carried out the condensations of cyclohexa- and cycloheptanone enolates. We give, in Table V, the best results.

Here, the yields are lower than in the synthesis of 5-diethylaminobenzofurans. The observed difference may have its origin together in the lower reactivity of **15** compared with that of **1**[11] and in the interference of some SNAr reaction of **1**.

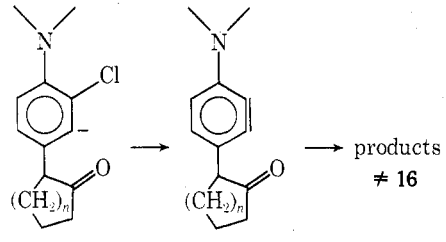
**Scheme VI**



**Scheme VII**




**Scheme VIII**



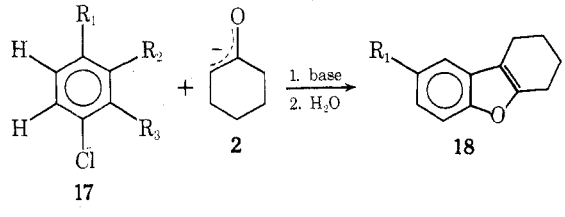

Moreover, a part of the ketocarbanionic intermediate may lose chloride ion more rapidly than prototropy occurs (Scheme VIII).

Formation of benzofuran **16** from the keto aryne thus generated is hardly likely.

## Conclusion

These cyclizations into benzofurans are, in fact, quite general. As an example, we have condensed cyclohexanone with the three following chloro derivatives: 3,4-dichloroanisole, 1,2- and 1,3-dichlorobenzene. The results are summarized in Scheme IX and Table VI.

**Scheme IX**




We need not emphasize the fact that this new application of the condensation of ketone enolates with arynes, adding to those we have described before,[12] is an interesting source of synthesis for widely diversified aromatic oxygenated heterocycles.

From a more particular point of view, 1,2,4- and 1,2,3-trichlorobenzene being the starting material in the synthesis of many dichlorinated dialkylanilines,[10] it appears that these trichloro derivatives of benzene may find versatile applications in synthesis.

## Experimental Section

Ir spectra were recorded with a Perkin-Elmer R 457 spectrophotometer; NMR spectra were carried out with Brucker HX 90 MHz, Varian A-60, or Jeol C-60 HL instruments; chemical shifts are given in $10^{-6}$ units with respect to $Me_4Si$ as internal standard. Analytical VPC was carried out at 220° with a Carlo Erba GI 452 instrument, flame-ionization detectors, SE-30 15% column (Chromosorb W DMCS). The silica gels used for liquid phase and thin layer chromatography were Kieselgel 0.05–0.2 mm and Kieselgel G (Merck), respectively. Eluents were petroleum ether (bp 45–60°)–ether mixtures. We used Fluka sodium amide, washed several times, and finely ground with a mortar, under solvent. Melting points (uncorrected) were measured with a platine. All new compounds have satisfactory carbon, hydrogen, nitrogen, and chlorine microanalyses and were submitted to referees.

**Table V**
**Cyclization of 15 (10 mmol) and 2 (27.5 mmol) in the Presence of Base in THF (130 ml)**

| Run | n | Base (mmol) | Conditions | 16, % |
|---|---|---|---|---|
| 17 | 2 | $NaNH_2$-*t*-BuONa (35–17.5) | 16 hr to 38° then 2 hr to 55° | 30 |
| 18 | 3 | $NaNH_2$-*t*-BuONa (35–17.5) | 21 hr to 45–50° | 11 |

**Table VI**
**Condensation of 17 and 2 in THF in the Presence of $NaNH_2$-*t*-BuONa[a]**

| Run | $R_1$ | $R_2$ | $R_3$ | Yield, % 18 |
|---|---|---|---|---|
| 19 | $CH_3O$ | H | Cl | 29 |
| 20 | H | Cl | H | 27 |
| 21 | H | H | Cl | 25 |

[a] For experimental conditions, see Experimental Section.

**General Procedure.** The quantities involved, as well as reaction times and temperature, are indicated in Tables I–VI. Operations were carried out with magnetic stirring, under nitrogen atmosphere.

The general procedure is exemplified with the following examples.

**Run 8 (Table II).** *t*-BuOH (55 mmol) in THF (10 ml) was added dropwise to a suspension of 125 mmol of $NaNH_2$ in THF (30 ml); the mixture was heated at 45–50° for 2 hr; the ketone (50 mmol) diluted in THF (10 ml) was added at a temperature <20°, and the mass was heated at 40° for 2 hr. The mixture thus obtained was heated to the desired temperature, and, after addition of 170 ml of THF, the reagent (18 mmol) diluted in THF (20 ml) was added dropwise (total quantity of THF 240 $cm^3$). After the end of the reaction, the mass was poured on ice, extracted with ether, and dried over $K_2CO_3$. After evaporation of the solvents under reduced pressure, the mixture was simply filtered over a silica gel column.

**Run 10.** To a suspension of $NaNH_2$ (115 mmol) in THF (30 ml), the ketone (50 mmol) diluted in THF (10 ml) was added at a temperature below 20°, and the mass was heated at 40° for 2 hr. The mixture being heated at the desired temperature, the reagent (18 mmol) was added dropwise with 50 ml of THF. After a time mentioned in Table II (3 hr at 20–25°) 60 $cm^3$ of HMPA, diluted in 90 $cm^3$ of THF, was added. After the end of the reaction (25 hr at 50°), the mass was poured onto ice, etc. (see above).

**Isolated Products.** 5-(*N*,*N*-Diethylamino)-2,3-trimethylenebenzofuran (**4**, $n = 1$): mp 29–30°; $n^{24}D$ 1.5822; NMR ($CDCl_3$) aliphatic H's 3.29 (q, $J = 7$ Hz, 4 H), 1.11 (t, $J = 7$ Hz, 6 H), 2.71 ppm (m, 6 H); aromatic H's, ABX spectrum, 7.26 (dd, $J = 8.7$, 1 Hz, 1 H), 6.60–6.75 ppm (three signals, 2 H). Irradiations at 3.29 and 2.71 ppm result in the sharpening of the peaks (6.60–6.75).

5-(*N*,*N*-Diethylamino)-2,3-tetramethylenebenzofuran (**4**, $n = 2$): see previous paper.

5-(*N*,*N*-Diethylamino)-2,3-pentamethylenebenzofuran: NMR ($CDCl_3$) aliphatic H's 3.29 (q, $J = 7$ Hz, 4 H), 1.10 (t, $J = 7$ Hz, 6 H), 2.83 (m, 2 H), 2.61 (m, 2 H), 1.77 ppm (m, 6 H); aromatic H's, ABX spectrum, 7.21 (d, $J = 8.5$ Hz, 1 H), 6.65–6.80 ppm (m, four signals, 2 H). Irradiations at 3.29 ppm result in the sharpening of the peaks (6.65–6.80).

5-(*N*,*N*-Diethylamino)-2,3-hexamethylenebenzofuran (**4**, $n = 4$): see previous paper.

5-(*N*,*N*-Diethylamino)-2-ethyl-3-methylbenzofuran (**9**, R =

$CH_3$): NMR ($CDCl_3$) aliphatic H's 3.30 (q, $J$ = 7.5 Hz, 4 H), 2.71 (q, $J$ = 7.5 Hz, 2 H), 2.11 (s, 3 H), 1.27 (t, $J$ = 7.5 Hz, 3 H), 1.11 ppm (t, $J$ = 7.5 Hz, 6 H); aromatic H's 7.20 (d, $J$ = 9.5 Hz, 1 H), 6.85–6.65 ppm (m, three signals, 2 H). Irradiations at 3.30 ppm result in the sharpening of the peaks (6.85–6.65).

5-(*N,N*-Diethylamino)-2-butyl-3-propylbenzofuran (**9**, R = *n*-$C_3H_7$): NMR ($CDCl_3$) aliphatic H's 2.0–0.65 (m, 18 H), 2.57 and 2.70 (2 t, $J$ = 7 Hz, 4 H), 3.32 ppm (q, $J$ = 7 Hz, 4 H); aromatic H's, ABX spectrum, 7.25 (d, $J$ = 8 Hz, 1 H), 6.83 (d, $J$ = 1.5 Hz, 1 H), 6.73 ppm (dd, $J$ = 8.5, 2.5 Hz, 1 H). Irradiations at 3.32 ppm result in the sharpening of the d (6.83) and the dd (6.73).

5-(*N,N*-Diethylamino)-2-isopropylidene-3-dimethyldihydro-2,-3-benzofuran (**11**): NMR ($CDCl_3$) aliphatic H's 3.23 (q, $J$ = 7 Hz, 4 H), 1.10 (t, $J$ = 7 Hz, 6 H), 1.52 (s, 6 H), 1.79 ppm (s, 6 H); aromatic H's, ABX spectrum, 6.73 (d, $J$ = 9.5 Hz, 1 H), 6.56 (d, $J$ = 2.5 Hz, 1 H), 6.52 ppm (dd, $J$ = 9.5, 2.5 Hz, 1 H); ir (film) $\nu_{C=C}$ 1705 $cm^{-1}$.

5-(*N,N*-Diethylamino)-1,3-tetramethylbenzo-3a,7a-cyclopentanone (**12**): NMR ($CDCl_3$) aliphatic H's 3.42 (q, $J$ = 7 Hz), 1.18 (t), 1.26 (s), 1.33 ppm (s) (18 H); aromatic H's 7.17 (d, $J$ = 8.25 Hz, 1 H), 6.85–6.50 ppm (m, three signals, 2 H); ir (film) 1750 $cm^{-1}$.

6-Morpholino-2,3-tetramethylenebenzofuran (**16**, $n$ = 2): mp 122–123°; NMR ($CDCl_3$) aliphatic H's 1.82 (m, 4 H), 2.62 (m, 4 H), 3.10 (m, 4 H), 3.82 ppm (m, 4 H); aromatic H's 7.27 (d, $J$ = 8.5 Hz, 1 H), 6.96 (d, $J$ = 2 Hz, 1 H), 6.85 ppm (dd, $J$ = 8, 2 Hz, 1 H). Irradiations at 3.10 ppm result in the sharpening of the d (6.96) and of the dd (6.85). Irradiations at 2.62 ppm result in the sharpening of the d (7.27).

6-Morpholino-2,3-pentamethylene-2,3-benzofuran (**16**, $n$ = 3): mp 109–110°; NMR ($CDCl_3$) aliphatic H's 1.80 (m, 6 H), 2.66 (m, 2 H), 2.88 (m, 2 H), 3.13 (m, 4 H), 3.86 ppm (m, 4 H); aromatic H's, ABX spectrum, 7.27 (d, $J$ = 8 Hz, 1 H), 7.0–6.8 ppm (m, AB part, three signals, 2 H). Irradiation at 3.13 ppm results in the sharpening of the AB part. Irradiation at 2.66 ppm results in the sharpening of the X part of the spectrum.

**Condensation of 17 (20 mmol) and 2 (40 mmol) in THF (260 $cm^3$) with $NaNH_2$ (40 mmol) and *t*-BuONa (20 mmol). Experimental conditions.** Run 19, 25 then 50°; 2.5 then 24 hr; runs 20 and 21, 25 then 50°; 1 then 3 hr.

5-Methoxy-2,3-tetramethylenebenzofuran (**18**, $R_1$ = $CH_3O$): NMR ($CDCl_3$) aliphatic H's 1.80 (m, 4 H), 2.60 (m, 4 H), 3.75 ppm (s, 3 H); aromatic H's, ABX spectrum between 6.60 and 7.35 ppm.

2,3-Tetramethylenebenzofuran (**18**, $R_1$ = H): NMR ($CDCl_3$) m between 1.5 and 1.2 (4 H), m (2.3–3, 4 H), m (7–7.75, 4 H).

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**Registry No.**—**1**, 55039-58-2; **2** ($n$ = 1), 55886-83-4; **2** ($n$ = 2), 55886-84-5; **2** ($n$ = 3), 55886-85-6; **2**($n$ = 4), 55886-86-7; **4** ($n$ = 1), 55886-87-8; **4** ($n$ = 3), 55886-88-9; **5** ($n$ = 1), 55886-89-0; **5** ($n$ = 2), 55886-90-3; **5** ($n$ = 3), 55886-91-4; **5** ($n$ = 4), 55886-92-5; **8** (R = $CH_3$), 55886-93-6; **8** (R = *n*-$C_3H_7$), 55886-94-7; **9** (R = $CH_3$), 55886-95-8; **9** (R = *n*-$C_3H_7$), 55886-96-9; **10**, 55886-97-0; **11**, 55886-98-1; **12**, 55886-99-2; **15**, 55039-67-3; **16** ($n$ = 2), 55887-00-8; **16** ($n$ = 3), 55887-01-9; **17** ($R_1$ = $CH_3O$; $R_2$ = $R_3$ = H), 623-12-1; **17** ($R_1$ = $R_3$ = H; $R_2$ = Cl), 541-73-1; **17** ($R_1$ = $R_2$ = H; $R_3$ = Cl), 95-50-1; **18** ($R_1$ = $CH_3O$), 7291-77-2; **18** ($R_1$ = H), 13130-19-3.

## References and Notes

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# High-Dilution Cyclization of Polyoxapentacosanodinitriles[1]

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The syntheses of 7,10,13,16,19-pentaoxapentacosanodinitrile (**4**), 8,13,18-trioxapentacosanodinitrile (**5**), and 5,9,13,17,21-pentaoxapentacosanodinitrile (**6**), and the Ziegler-type cyclization of these nitriles by an improved method, are described. The cyclized products were converted into 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 8,13,18-trioxacyclotetracosanone (**3**), and 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), respectively. From **1**, **2**, and **3** were prepared the amino alcohols 1-piperidinomethyl-7-10-13-16-19-pentaoxacyclotetracosanol (**26**), 1-piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (**27**), and 1-piperidinomethyl-8,13,18-trioxacyclotetracosanol (**28**), respectively. By reduction of the ketonitrile obtained by the cyclization of **5**, there was obtained 2-aminomethyl-8,13,18-trioxacyclotetracosanol (**29**). The amino alcohols **26–29** were screened for biological activity with negative results.

In this paper the syntheses of 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), and 8,13,18-trioxacyclotetracosanone (**3**), and derivatives thereof, are described. These compounds were desired as possible components of catena and rotaxane type compounds.[4] The novel catena compounds hoped for would be of interest for testing as to their pharmacological activity inasmuch as the two functional groups would be on different rings, e.g., hydroxyl on one ring, amino on the other, which by rotating could put the functions at different distances from each other. In previous examples of catena compounds, polymethylene chains were used almost exclusively in the construction of the desired large rings. We were interested in including oxygen atoms in the chain for three reasons: (a) the presence of oxygen atoms might make possible the attainment of yields of catenas and rotaxanes higher than those heretofore obtained by statistical methods;[5,6] (b) the resulting compounds would be more