Aryne and S_NAr Reactions of Polyhalogenobenzenes. 6.† Synthesis of Benzofurans

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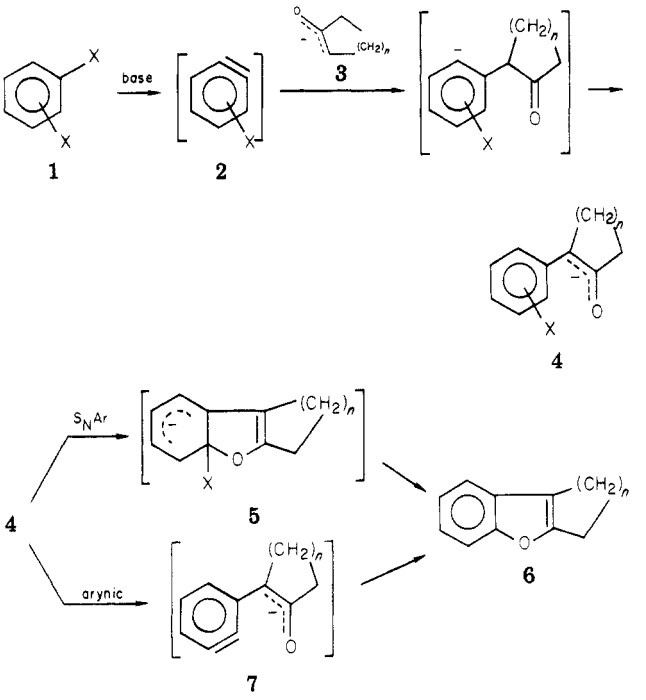
The scope and limitations of the one-pot synthesis of benzofurans by aryne condensations of the cyclic ketone enolates with dihalogenobenzenes in the presence of the complex base $NaNH_2$–*t*-BuONa were studied. It is shown that this method is of interest for the synthesis of a large variety of benzofurans. A new, simple, and selective monodealkylation of (dialkylamino)benzene derivatives by chloroethyl chloroformate is reported.

The benzofuran nucleus is a common one in natural substances[1] as well as in synthetic products with pharmacological applications.[2] This ubiquity explains the large number of papers devoted to the synthesis of this important heterocycle.[3,4]

On the other hand, considering the large diversity of structures containing the benzofuran skeleton, none of the synthetic methods published are completely general (inconsistency of functional groups with the reaction conditions, low overall yields of multistep pathways, time consuming starting material preparation; for a critical review see ref 5). Thus is appears that any new synthetic method is of interest in enhancing the possibilities offered to the chemist in this field.

Some years ago, we described the first results obtained in the study of a new approach to the synthesis of the benzofuran ring and involving the aryne and S_NAr condensation of ketone enolates with *o*-dichlorobenzene derivatives using $NaNH_2$ or the complex base $NaNH_2$–*t*-BuONa as basic reagents.[6,7] In the present paper we delineate the scope and limitations of our synthesis with cyclic ketone enolates as well as further extensions of these reactions. Recently Kobayoshi published the synthesis of polyfluorobenzofurans by S_NAr condensation of very reactive hexafluorobenzene with ketone enolates.[8]

Scheme I



Results and Discussion

Condensation of Cyclohexanone Enolate with Dihalogenobenzenes in the Presence of the Complex Base $NaNH_2$–*t*-BuONa. From our previous work, it appeared that aryne and S_NAr mechanisms are involved during the formation of a benzofuran from dihalogenobenzenes. The possible pathways are exemplified on Scheme I.

It is well-known that aryne as well as SNAr reactions of ketone enolates are strongly dependent on the nature of both the aryl halide and the starting ketone. Moreover, aryne formation is also strongly dependent on the nature of the base used. Finally, it must be noted that SNAr condensations from **4** require the presence of the halogen at the ortho position, while an aryne reaction may occur with the halogen at the ortho as well as the meta positions.

Taking these considerations into account, we decided to systematically investigate the condensations of representative dihalogenobenzenes on representative cyclic ketone enolates. From a series of preliminary experiments performed with *o*-dichlorobenzene and cyclohexanone enolate, it appeared that the best results (see Experimental Section) were obtained at 40 °C in THF with the complex base $NaNH_2$–*t*-BuONa under a slow stream of nitrogen or argon (the yields were lower when the inert atmosphere stream was removed !). The best relative ratio of reagents was determined as being 1/2/3/6 aryl halide/sodium ketone enolate/*t*-BuONa/$NaNH_2$.

As usual,[6,7] the excess ketone may be nearly quantitatively recovered at the end of the condensation. However, reasonable yields were obtained only when a minimal excess of ketone enolate was present during the condensation. This observation has been made in the pioneering work of Leake and Levine[9] as well as our own[10] but has never received any explanation!

With these data in hand, we studied the condensation of a series of aryl dihalides chosen from among the most readily available. The results are summarized in Table I and deserve some comment.

† See ref 7 for part 5.

(1) F. M. Dean, "Naturally Occuring Oxygen Ring Compounds", Butterworths, London, 1963, p 535.
(2) R. Royer, "Pharmacochimie du benzofuranne, Actualités de Chimie Thérapeutique", Société de Chimie Thérapeutique, 1975, Series 3e.
(3) P. Cagniant and D. Cagniant, *Adv. Heterocycl. Chem.*, 18, 337 (1975).
(4) A. Mustafa, *Chem. Heterocycl. Compd.*, 29, 1 (1974).
(5) R. Royer, *Khim. Geterosikl. Soedin.*, 579 (1977).
(6) P. Caubere and L. Lalloz, *J. Org. Chem.*, 40, 2853 (1975).
(7) P. Caubere and L. Lalloz, *J. Org. Chem.*, 40, 2859 (1975).
(8) Y. Inukay, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, 52, 2657 (1979).
(9) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, 81, 1169 (1959).
(10) P. Caubere and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 3857 (1968).

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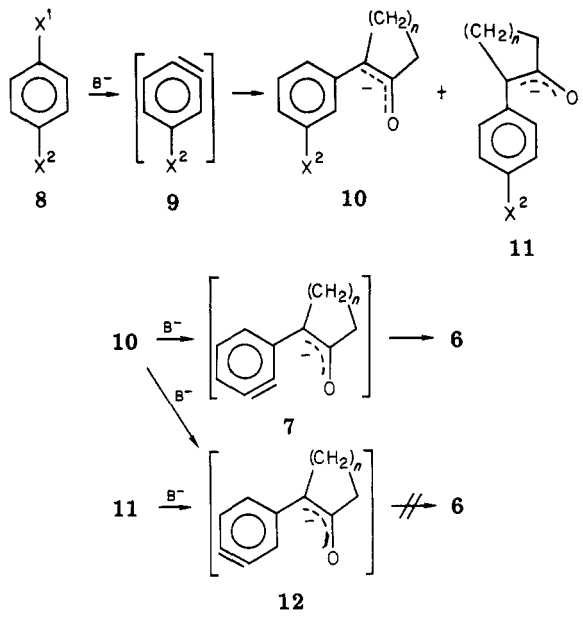
Table I. Condensation of Aromatic Dihalides on Cyclohexanone Enolate at 40 °C in THF in the Presence of $NaNH_2$-t-BuONa

aryl halide	reaction time, h	% yield of 6 ($n = 3$)[a,b]
1,2-$Cl_2C_6H_4$	5	30
1,3-$Cl_2C_6H_4$	3	31
1,4-$Cl_2C_6H_4$	9	24
1,2-$Br_2C_6H_4$	5	19
1,3-$Br_2C_6H_4$	3	22
1,4-$Br_2C_6H_4$	6	28
1,2-Br,Cl-C_6H_4	5	29
1,3-Br,Cl-C_6H_4	4	35
1,4-Br,Cl-C_6H_4	9	30
1,2-Br,F-C_6H_4	2	39
1,3-Br,F-C_6H_4	2	45
1,4-Br,F-C_6H_4	2	49
1,4-Cl,F-C_6H_4	2	47
1,4-I,F-C_6H_4	4	47
1,4-I,Cl-C_6H_4	4	22
1,4-I,Br-C_6H_4	5	35

[a] Named 6b (vide infra), oil. [b] Satisfactory analyses (±0.4% for C and H) were obtained.

Scheme II



It is noteworthy that 1,4-dihalogenobenzenes led to yields which, generally speaking, compare favorably with those obtained from 1,2- and 1,3-derivatives. With the para-substituted derivatives, the most general reaction that could be written is described by Scheme II.

The data indicate that a second aryne step must be involved in the ring closure. On consideration of the different possible pathways, yields obtained with p-difluoro-, p-chlorofluoro-, p-bromoiodo-, and p-fluoroiodobenzenes are rather surprising. Indeed, if we admit that the probability for the formation of 10 and 11 is the same, the yield of 6 could only reach a maximum of 50%. Yields of 47–49% seem to show that some unexpected directing effect favors the condensation in the meta position relative to X^2.

With fluoro derivatives, quenching the reaction before completion showed that the remaining halogen X^2 was fluorine,[11] in agreement with the low reactivity of the carbon–fluorine bond[12] but in contradiction with the enhancing hydrogen acidity effect of fluorine in the ortho position.[13]

With o- and m-dihalogenobenzenes (13 and 16) the situation is still more complicated (Scheme III). The only possible aryne from 13 is 14, which is also the predominant (if not the only) one from 16. The higher reactivity of 16 (compared to 13) could be due to a more acidic proton located between the two halogens, enhancing the propensity to give an aryne.

Now, 10 must be formed from 14 in larger amounts than 15.[14,15] However, it must be recalled that the formation of 10 must involve the carbanion 10a which may rapidly eliminate X^{2-} (this elimination may be synchronous with the condensation of the ketone enolate on 14), leading to the formation of the corresponding benzyne evolving toward side products. This could explain why 1,4-dihalides may lead to comparable or even better results than 1,2- or 1,3-derivatives.

In conclusion, it appeared that 1,4-dihalogenzenes constitute the best starting materials, and among them, parafluorobromobenzene seems of particular interest.

Effect of Ketone Structure. On consideration of the numerous studies performed in our laboratory on aryne condensations with ketone enolates,[16] it appeared that the structure of the starting ketone generally has a strong effect on the result of the reactions. Thus, it was decided to briefly investigate this effect on the aryne synthesis of benzofurans. The main results are summarized in Table II.

Yields were very low with cyclooctanone, and from experiments not reported here, it appeared that no benzofurans were formed on starting from the larger ketonic ring. Moreover, results reported in Table II show that the presence of substituents on the ketone ring tends to lower the yields of benzofurans.

The data given above imply that these reactions do not constitute good syntheses of benzofurans. However, it must be borne in mind that these one-pot reactions make use of easily available starting materials and may be performed on a large scale. The yields compare favorably with overall yields of usual multistep syntheses,[17,18] but our condensations are much less time consuming.

Effect of Additional Substituent. Substituted benzofurans bearing a reactive group on the benzo ring are of interest in view of further applications.[1-5] However, reactive functions on the aromatic ring are not generally consistent with aryne reactions, and protected functions must be used.

On the other hand, we have previously shown[6,7] that (diethylamino)benzofurans might be obtained from 1,2-dichloro-4-(diethylamino)benzene.

Taking these observations into account, we decided to extend our benzofuran synthesis to a few 1,2-dichlorobenzenes substituted by masked RNH, NH_2, and HO groups and to examine the release of the free functions on the benzofurans formed.

Some representative syntheses of benzofurans substituted on the aromatic ring by masked functions have been gathered in Table III.

These results deserve some brief comments. Comparison of the yield obtained with $Z^1 = Me_2N$ with those

(11) M. Ibrahim, Thèse, University of Nancy, France, 1981.
(12) F. L. Scott and R. E. Oesterling, *J. Am. Chem. Soc.*, **82**, 5247 (1960).
(13) H. Heaney, *Chem. Rev.*, **62**, 81 (1962).
(14) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, 1967.
(15) E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).
(16) P. Caubere, *Top. Curr. Chem.* **75**, 50 (1978).
(17) F. Ebel, *Helv. Chim. Acta*, **12**, 3 (1929).
(18) T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966).

Scheme III

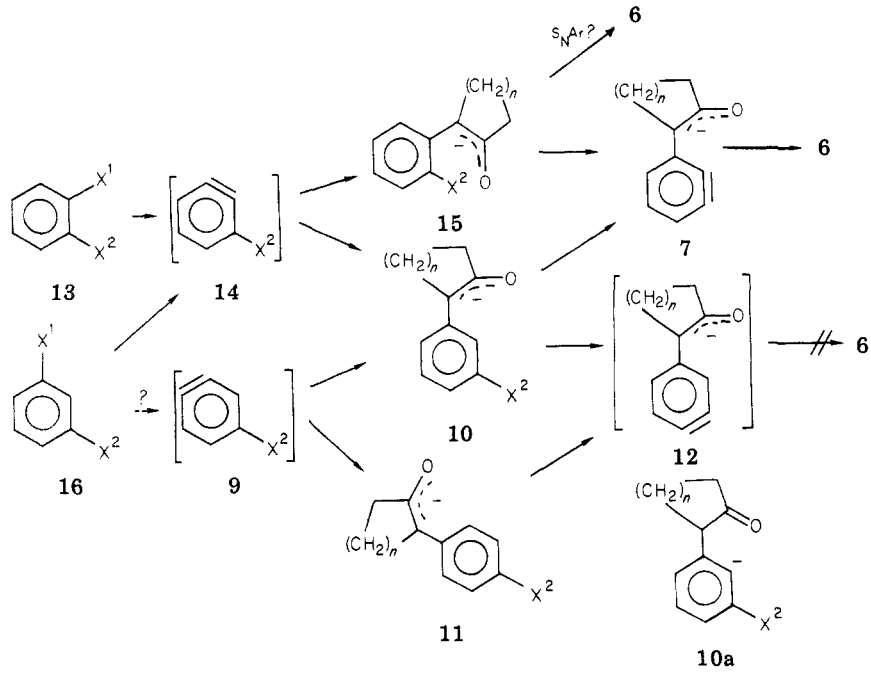
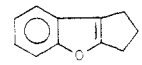
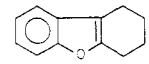
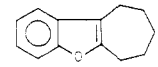
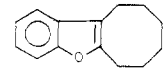
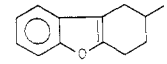
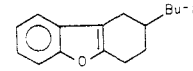
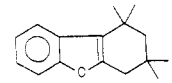
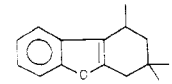


Table II

1-fluoro-4-bromobenzene —(ketone enolate, $NaNH_2$-*t*-BuONa, THF, 40 °C)→ benzofuran

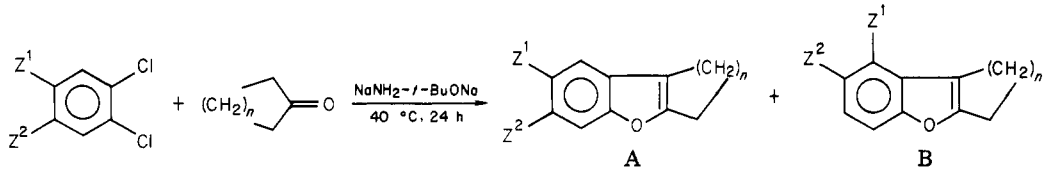
ketone	reaction time, h	benzofuran[a]	no.	% yield	mp, °C
cyclopentanone	4		6a	10	oil
cyclohexanone	4		6b	47	oil
cycloheptanone	4		6c	14	oil
cyclooctanone	6		6d	4	oil
4-methylcyclohexanone	6		17	23	oil
4-*tert*-butylcyclohexanone	30		18	25	oil
3,3,5,5-tetramethylcyclohexanone	20		19	11	55
3,3,5-trimethylcyclohexanone	20		20	20	oil

[a] Satisfactory analyses (±0.3% for C and H) were obtained.

previously obtained with $Z^1 = Et_2N$[6,7] shows comparable behavior of the corresponding aryl halides. On the contrary, when the dialkylamino group was replaced by a dibenzylamino group, the yields were lower. In all cases, the strong meta-directing effect of nitrogen[14,15] led to the formation of benzofurans of the **A** type only. Methoxy and tetrahydropyranyloxy groups exhibit the same effect and led to mixtures of benzofurans A and B according to the lower meta-directing effect of oxygen compared to nitrogen. However, as expected, benzofurans A arising from meta condensations were the main products.

Finally, the free functional benzofurans were obtained by removal of blocking groups (Table IV and Scheme IV). Tetrahydropyranyloxy easily liberated the corresponding hydroxyl group in classical acidic conditions. Starting from the mixture of benzofurans obtained by aryne condensations, we easily isolated each of the unprotected derivatives in quantitative overall yields. Methoxy benzofurans necessitated more drastic conditions. As exemplified for two cases in Table IV, Jung's method[19] improved by Olah et

Table III

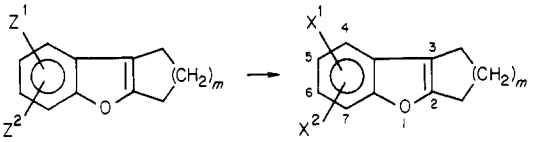


A B

				rel amt[c]		mp, °C	
Z^1	Z^2	n	overall yield, %	A (% yield)	B (% yield)	A	B
Me_2N	H	3	50	**21** (100)		38	
$(PhCH_2)_2N$	H	2	25	**22** (100)		92	
$(PhCH_2)_2N$	H	3	22	**23** (100)		79	
$(PhCH_2)_2N$	H	4	21	**24** (100)		51	
MeO	H	2	23	**25a** (65)	**25b** (35)	81	79
MeO	H	3	40	**26a** (80)	**26b** (20)	32	36
MeO	H	4	28	**27a** (75)	**27b** (25)	oil	71
THPO[a]	H	2	23	**28a** (70)[b]	**28b** (30)[b]		
THPO[a]	H	3	44	**29a** (78)[b]	**29b** (22)[b]		
THPO[a]	H	4	27	**30a** (80)[b]	**30b** (20)[b]		
MeO	MeO	3	30	**31** (100)		129	

[a] THP = tetrahydropyranyle. [b] Determined after removal of THP. [c] Satisfactory analyses (±0.4% for C and ±0.2% for H and N) were obtained.

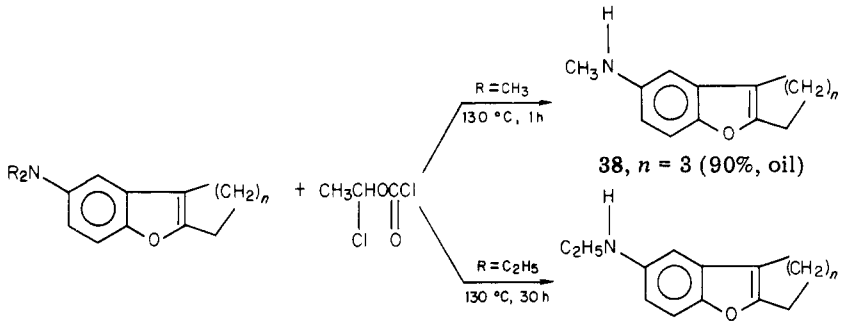
Table IV



starting benzofurans[a]	conditions	X^1, X^2, product (yield %)[b]	mp, °C A	mp, °C B
28a + **28b**	H_3O^+, 20 °C, 3 h	5-OH, H, **32a** (71) + 4-OH, H, **32b** (29)	114 (**32a**)	133 (**32b**)
29a + **29b**	H_3O^+, 20 °C, 3 h	5-OH, H, **33a** (78) + 4-OH, H, **33b** (22)	107 (**32a**)	82 (**33b**)
30a + **30b**	H_3O^+, 20 °C, 3 h	5-OH, H, **34a** (80) + 4-OH, H, **34b** (20)	134 (**34a**)	141 (**34b**)
26a	Me_3SiCl, NaI, CH_3CN, 70 °C 30 h	5-OH, H, **33a** (82)	107	
27a	Me_3SiCl, NaI, CH_3CN, 70 °C 30 h	5-OH, H, **34a** (84)	134	
31	$C_5H_5NH^+$, Cl^-, 200 °C, 5 min	5-OH, 6-OH, **35** (91)	123	
23	H_2-Pd/C, 20 °C, EtOH, 3 h	5-NH_2, H, **36** (96)	71	
24	H_2-Pd/C, 20 °C, EtOH, 3 h	5-NH_2, H, **37** (95)	78	

[a] Formula given in Table III. [b] Satisfactory analyses (±0.4% for C, H, and N) were obtained.

Scheme IV



38, n = 3 (90%, oil)

39, n = 2 (79%, mp 93 °C)
40, n = 3 (90%, oil)
41, n = 4 (89%, mp 59 °C)

al.[20] was very convenient. However, this reaction did not lead to good results with dimethoxy benzofuran and the method developed by Royer et al.[21] was preferred. Turning toward amino benzofurans, we obtained free amino groups from dibenzylamino derivatives by classical hydrogenolysis on a palladium catalyst except for **22** (n = 2) which led to an instable product!

Obtention of (alkylamino)benzofurans necessitated, of course, completely different conditions. We were inspired by the method developed by Olofson[22] for dealkylation of tertiary amines.

We found that on using the inexpensive reagent chloroethyl chloroformate instead of vinyl chloroformate and

(19) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
(20) G. A. Olah, S. C. Narang, B. G. Balaram Gupta, and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).
(21) R. Royer, J. P. Buisson, P. Demerseman, and A. Cheutin, *Bull. Soc. Chim. Fr.*, 3647 (1970).
(22) R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, *Tetrahedron Lett.*, 1563 (1977).

operating without a solvent, demethylations as well as deethylations could be easily performed in good yield.

Conclusion

Examination of our results shows that the present aryne synthesis of benzofurans is not a general one but allows the rapid preparation of numerous and varied such heterocycles (more than 20 of the compounds prepared were unknown). It favorably compares with the multistep syntheses described in the literature since it involves one-pot reactions and starting from easily available starting materials and is achievable on a large scale. Thus, these condensations nicely enhance the potential methods of benzofuran synthesis.

Moreover, the new monodealkylation of dialkylamino aromatic derivatives may be helpful in synthesis since it allows selectively recovering an Ar–NHR substrate from $Ar–NR_2$, and we are actively studying this point.

Experimental Section

General Methods. See the paragraph at the end of the paper about supplementary material. ^1H NMR spectra were recorded with either a Perkin-Elmer R 12 B (60 MHz) or a Cameca 250 (250 MHz) spectrometer using Me_4Si as an internal standard and are reported as parts per million (δ). IR spectra were obtained with Perkin-Elmer R 457 and 225 instruments. UV spectra were carried out with a Varian-Techtron 635 spectrometer.

GLC analyses were carried out at 200–250 °C with a Girdel Model 75 CD/PT instrument with a 15% SE-30 column (Chromosorb W DMCS). The silica gels used for liquid phase and thin layer chromatography were Kieselgel (0.063–0.200 mm) and Kieselgel G (Merck), respectively, with petroleum ether (bp 45–60 °C)–diethyl ether mixtures as eluents.

Materials. Fluka sodamide was washed several times with THF and finely ground with a mortar under THF. Badische Anilin reagent grade THF freshly distilled from a benzophenone–sodium couple was used.

All melting points (Kofler) reported are uncorrected.

General Procedure for the Preparation of Benzofurans. Reaction times are indicated in Tables I–III. Reactions were carried out with magnetic stirring under a nitrogen or argon atmosphere. Reactions were monitored by GLC and/or TLC analysis.

A solution of *t*-BuOH (60 mmol) in THF (10 mL) was added dropwise to a suspension of $NaNH_2$ (220 mmol) in THF (30 mL), the mixture was heated at 40 °C for 1.5 h, the ketone (40 mmol) dilutes in THF (10 mL) was added at room temperature, and the reaction mixture was heated at 35–40 °C for 1.5 h. A solution of the dihalogenobenzene derivative (20 mmol) in THF (50 mL) was then added and, in all cases, the mixture thus obtained was heated at 40 °C for the required times. Upon completion, the mass was poured on ice, extracted with diethyl ether or methylene chloride, washed twice with water, and dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the different components of the mixture were separated by chromatography on a silica gel column.

Typical Procedure for Cleavage of Tetrahydropyranyl Groups. To a solution of (tetrahydropyranyloxy)benzofuran (5 mmol) in acetone (10 mL) was added HCl (10%, 2 mL). The mixture was allowed to stand at room temperature. After the end of the reaction (monitored by TLC) the mixture was poured into water, extracted with diethyl ether, washed, and dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the different components of the mixture were separated by chromatography through use of a silica gel column. The overall yield was 100% (see Table IV).

Demethylation of 26a and 27a. To a solution of the corresponding methyl ether (5 mmol) and sodium iodide (7.5 mmol) in acetonitrile (10 mL) was slowly added chlorotrimethylsilane (7.5 mmol) with continuous stirring. The mixture was stirred at 70 °C up to completion of the reaction, as monitored by TLC. At the end of the reaction, the mixture was quenched with water (50 mL) and extracted with diethyl ether. The organic layer was washed with sodium thiosulfate and then water and dried over $MgSO_4$. Evaporation of the solvents gave phenolic products which were recrystallized from cyclohexane (see Table IV).

Demethylation of 31. Compound **31** (5 mmol) was treated by pyridinium chloride (25 mmol) at 180–200 °C. After 5 min, the reaction mixture was poured on ice and taken up in ether. Evaporation of the solvent gave pure **35** (See Table IV).

Catalytic Hydrogenation of Dibenzylamino Derivatives. (Dibenzylamino)benzofuran (1.0 g) dissolved in ethanol (15 mL) was hydrogenated in the presence of Pd/C (10%, 500 mg) for 3 h. The catalyst was filtered off and the solvent removed under reduced pressure to afford the aminobenzofuran which was purified by chromatography on a silica gel column (see Table IV).

Typical Monodealkylation of Dialkylamino Derivatives. The dialkylaminobenzofuran (1 g) was dissolved in an excess of 1-chloroethyl chloroformate (5 g) and the mixture was heated at 130 °C for the required time (Scheme IV). The reaction was monitored by GLC analysis. At the end of the reaction, methanol (10 mL) was added at room temperature, and the mixture was allowed to stand at 40 °C for 1 h. It was then treated by NaOH (5%, 100 mL) and extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The monoamino derivative was separated by chromatography on a silica gel column.

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Supplementary Material Available: Full NMR, IR, and UV data for all prepared benzofurans (5 pages). Ordering information is given on any current masthead page.