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A STEREOSPECIFIC SYNTHESIS OF 9,11-AZO-PGH_1 DERIVATIVES - POTENTIAL INHIBITORS OF BLOOD PLATELET AGGREGATION

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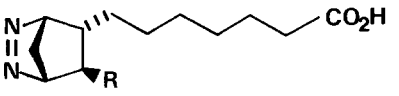
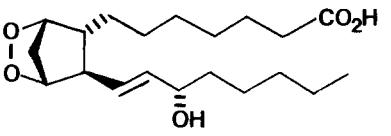
Abstract The stereospecific synthesis of the novel 9,11-azo-PGH_1 analogues 2 and 3 from the bicyclic intermediate 9 is reported

The 9,11-azo-PGH_1 analogue 1 is a potent inhibitor of human blood platelet aggregation which acts by blocking both thromboxane A_2 (TXA_2) synthetase and the PGH_2/TXA_2 receptors [1] Interestingly, the simple bicyclic compounds 4 and 5, which lack both side chains, also exhibit anti-aggregatory activity[2] whereas certain analogues lacking only the top side chain are inactive.[3] These findings prompted us to report our own work in this area and we describe herein a synthesis of the novel 9,11-azo-PGH_1 analogues 2 and 3 which lack the bottom side chain and the 15-hydroxy group of 1 respectively The synthesis proceeds via the key intermediate 9 which is easily prepared and purified on a large scale without recourse to tedious chromatography (cf. ref. 1) and can be used to prepare a variety of related analogues including the known[1] TXA_2 'synthetase inhibitor/receptor blocker'

Clearly analogues 2 and 3 will provide a deeper insight into the structure-activity relationship of this class of compound which in turn will define future objectives in the search for anti-thombotic drugs

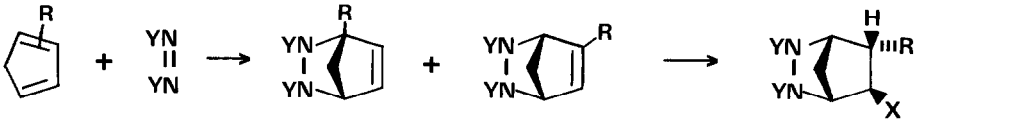


1 R = $OCH_2CH(OH)(CH_2)_4CH_3$
2 R = H
3 R = $O(CH_2)_6CH_3$



PGH_1

	X-X
4	O-O
5	N=N



6 7 8 9 10 X = H; 11 X = OH; 12 X = O(CH$_2$)$_6$CH$_3$

R = (CH$_2$)$_6$CO$_2$CH$_3$ Y = CO$_2$CH$_3$

Sequential treatment of cyclopentadiene with methyllithium (0.95 equiv., THF, 0°, 0.5 h) followed by methyl 7-bromoheptanoate (0.8 equiv., 23°, 4 5 h) afforded a mixture of the 2- and 3-alkylated cyclopentadienes 6 in 83% yield Treatment of crude 6 with dimethyl azodicarboxylate 7 (0 95 equiv., ether, 23°, 6 h) gave a 43 57 mixture of the two isomeric adducts 8 and 9 in quantitative yield. Separation of the required isomer 9 was achieved by simply cooling a solution of the isomeric mixture in ether (0 8 ml/g) at -4° for one to seven days which gave a crystalline precipitate of 9 Filtration followed by one recrystallisation from ether afforded 9 both isomerically and analytically pure[4] in 45% yield from 6 (78% recovery) [m p 70-71°, NMR/CDCl$_3$ δ6 03 (1H, bs, C=CH), δ5 04 (1H, bs, ⩾CH), δ4 98 (1H, bs, ⩾CH), δ3.77 (6H, s, CH$_3$O$_2$CN), δ3 65 (3H, s, CO$_2$CH$_3$), δ1 77 (2H, m, ⟨CH$_2$⟩), ν_{max}/cm^{-1} 1730, 1720, 1700, TLC (silica, ether) R_f 0 53 - red colour with phosphomolybdic acid (PMA), cf isomer 8 R_f 0 61 - blue colour with PMA]

Catalytic hydrogenation of 9 (Pd, THF) gave the reduced compound 10 (99%) derived from the *cis*-addition of hydrogen to the least hindered *exo*-face of 9[5] Hydrolysis of 10 (KOH, HO(CH$_2$)$_2$OH, 120°, 5 h) followed by the addition of excess aq. CuCl$_2$ at pH 7 afforded the copper complex of 2 as an insoluble red precipitate Treatment of this complex with aq NaOH liberated the required analogue 2 [m.p. 68-69°] in 76% yield from 9 Hydroboration - oxidation[6] of 9 afforded the *exo, trans*-alcohol 11 [85%, m p 67-68°] which was treated sequentially with NaH (2 equiv , DMSO, 30°, 0 5 h) followed by 1-iodoheptane (4 equiv , 23°, 7 h) to give 12 (55%) Hydrolysis of 12 followed by oxidation, as described above, gave the analogue 3 (51%) as a pale-yellow oil Biological evaluation of 2 and 3 will be reported at a later date [7]

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SOME PECULIAR CASES OF 7-TELESUBSTITUTION BY ANIONIC PHOSPHORUS NUCLEOPHILES ON 2-HALOTROPONES

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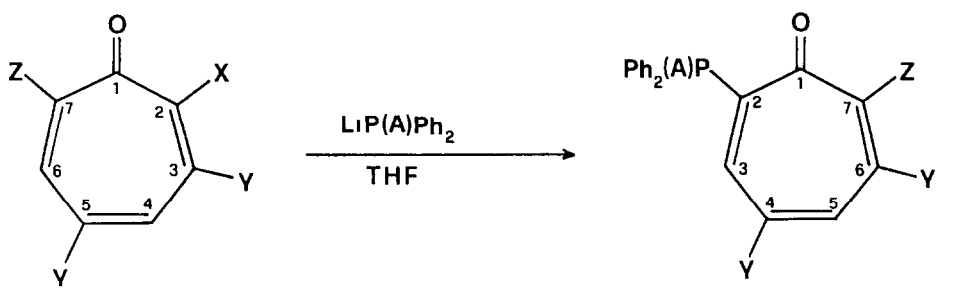
Summary Both 2-chloro- and 2-fluoro[3,5,7-$^2H_3$]tropone were found to react with lithium diphenylphosphide in tetrahydrofuran to give 2-diphenylphosphino[4,6-$^2H_2$]tropone in what constitutes the first example of telesubstitution by an anionic nucleophile in a non-protic solvent on tropones carrying nucleofugal groups, lithium diphenylphosphide oxide showed the same behaviour.

In the course of our search for novel covalent adducts between bases and troponoids,[1] we needed a tropone carrying a dialkyl- or a diarylphosphino group at C-2.[2]

We report here on the synthesis of such an intermediate from 2-halotropones and lithium diphenylphosphide which reveals peculiar cases of nucleophilic 7-telesubstitution with troponoids.



1a, X = Cl, Y = H, Z = H
1b, X = Cl, Y = D, Z = D
1c, X = F , Y = H, Z = H
1d, X = F , Y = D, Z = D

2a, Y=Z=H, A=nil
2b, Y=D (and partial deuteriation at C-7), A=nil
2c, Y=Z=H, A=O
2d, Y=D (and partial deuteriation at C-7), A=O

Thus, to 2-chlorotropone[§] (1a) (0.504 g, 3 6 mmol) in tetrahydrofuran[✧] (10 ml) was added, dropwise, at room temperature under nitrogen, slightly less than one molar equivalent of lithium diphenylphos

phide (LiP Ph_2) ◊ The mixture, which immediately turned to yellow-brown, was evaporated in vacuo to leave a tarry residue which was chromatographed on a Merck Kieselgel 60 P_{254} silica gel plate, 2 mm thick, eluant ethyl ether. The R_F 0 7 band gave 2a (0.45 g, yield 43%, based on the starting 1a) ‡ yellow crystals, mp 139-140°C, † uv, $\lambda_{max}^{CH_3OH}$ 224, 306 nm, log ε= 3 5, 2 8, ^{1}H nmr, ‡ δ (C_6D_6) = 7 4 (4H,m), 7 0 (6H,m), 7-6 (5H,m), ^{13}C nmr, δ ‡ 186.73, 187.44, Δδ=-0.71 (d, ^2J(PCC) = 16 5, 16 8, C-1), 139 54, 139 76, Δδ=-0 22(d, ^2J(PCC)= 4 8, 5.2, C-3), 138 33, 139 66, Δδ=- 1.33 (d, ^3J(PCCC)= 2.7, 2.7, C-7), 135.42, 137 68, Δδ= - 2 26 (d, ^1J(PC) = 13 3, 12 8, C-2), 135.21, 135 06, Δδ=0.15 (poorly resolved d, C-4), 133.32, 133 36, Δδ=- 0 04 (d, ^4J(PCCCC) = 2.6, 2 9, C-5), (the signal for C-6 in $(CD_3)_2CO$-$CDCl_3$ was obscured by a phenyl resonance at 132 82), 133.10, Δδ= -0 3 (s,C-6), and four phenyl resonances, ms (EI, 70 eV), m/e(%) = 292 (3.1), 291 (21.2),290 (100). These ^{13}C nmr data are in accordance with structure 2a In particular, the two largest differential shifts (Δδ) allow us to assign the two carbons in the α-position to the carbonyl group.[3] Moreover, all other assignments are compatible with known trends for carbon to phosphorus coupling.[3] The data below for the deuteriated analogue 2b confirm this assignment.

Starting from 2-fluorotropone[§] (1c), under the same conditions used for 1a, we obtained 2a in a lower, ca 10%, yield (based on the starting 1c) ‡ Both in this and in the above case no other troponoidal compound could be detected besides 2a

The reaction of 2-chloro[3,5,7-$^2H_3$]tropone[4,§] (1b) with lithium diphenylphosphide, under identical conditions to those used for 1a and 1c, gave 2-diphenylphosphino[4,6-$^2H_2$]tropone (2b), partially (ca 20%) deuteriated at C-7, ✕ yellow crystals, mp 140°C, † in a ca 10% yield, ms(EI, 70 eV) m/e (%) = 294(8 2), 293(44 7), 292(100), uv spectrum identical to that of 2a Starting from 2-fluoro-[3,5,7-$^2H_3$]tropone[4,§] (1d), under the same conditions used for 1c, the yield of 2b was low, as in the case of 2a from 1c, while the extent of deuteriation at C-7 was high (ca.60%), ms(EI, 70 eV), m/e(%)= 294(19), 293(80), 292(100) In the reaction mixtures obtained from either 1b or 1d we could not detect any other troponoidal compound besides 2b

In accordance with complete deuteriation at both C-4 and C-6, the ^{13}C nmr spectra of 2b in either 1 2 $(CD_3)_2CO$-$CDCl_3$ or C_6D_6 revealed only extremely weak, broad resonances at the values attributed to C-4 and C-6 for 2a Structure 2b is also fully supported by the results in the accompanying paper[2]

Similar results were obtained with 1a or 1b and lithium diphenylphosphide oxide (LiP(A)Ph_2= Li P(O)Ph_2) to give, respectively, 2-diphenylphosphinyltropone (2c), mp 173°C, † and 2-diphenylphosphinyl[4,6-$^2H_2$] tropone (2d), mp 172°C, in 21% and 13% yields, based on starting 1 Structures 2c and 2d are fully supported by the ^{13}C nmr spectra in 1 2 $(CD_3)_2CO$-$CDCl_3$. In particular, for 2c, δ=184 8 (d, ^2J(PCC) = 22 0, C = O), 145 1 (d, ^2J(PCC) = 6 7, C-3), 142.5 (d, ^3J(PCCC) = 5 8, C-7), 137 3 (d, ^4J(PCCCC) = 1 1, C-5), 135.5 (s,C-6), 133 1(d, ^3J(PCCC)= 16.7, C-4). For 2d, in accordance with complete deuteriation at both C-4 and C-6, and partial deuteriation at C-7, no signals were de-

tectable for either C-4 or C-6, while the doublet for C-7 (δ=142.5, ^{3}J(PCCC) = 5 7) was much weaker, and broadened, than with 2c

The whole body of the above results can be rationalized by the mechanism in the Scheme which, for simplicity, is drawn for the case of lithium diphenylphosphide only. According to this mechanism, the halogen X activates attack at C-7 by $Ph_2P^{\ominus}$, to give the intermediate 3 [5] That this

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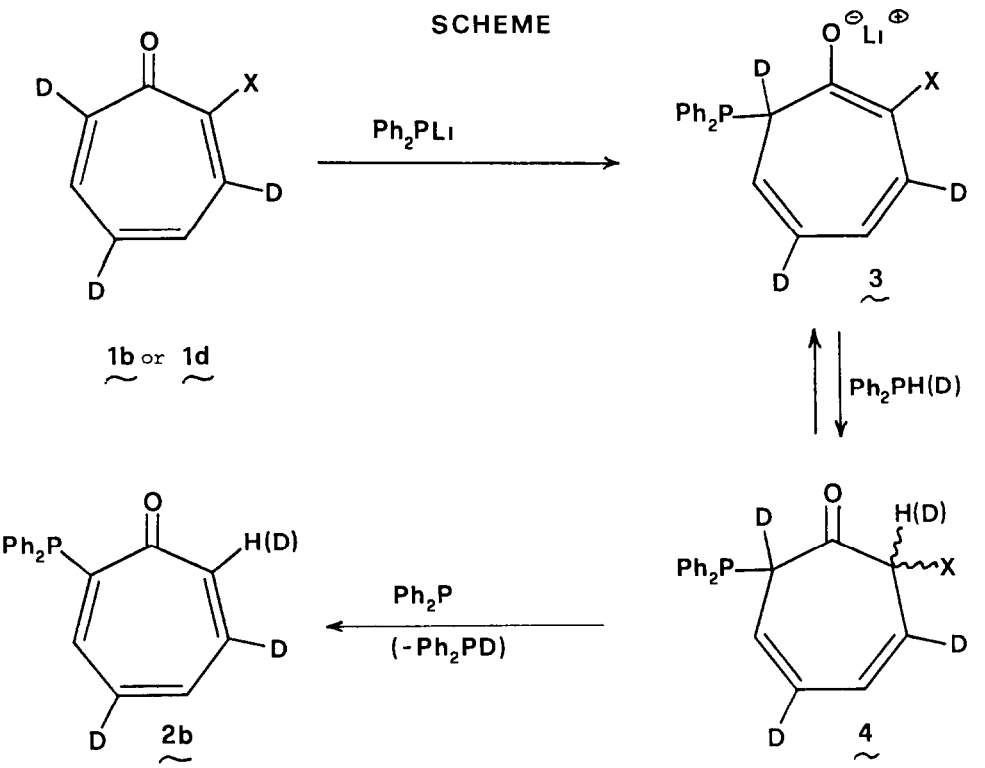

step cannot be reversible is in accordance with the extremely low nucleofugic aptitude of $Ph_2P^{\ominus}$. Therefore, 3 can only await for protonation at C-2 to give 4 We propose that the actual protonating agent is, at the beginning, Ph_2PH, generated by the reaction of $Ph_2P^{\ominus}$ with traces of moisture Elimination of DX from intermediate 4 by the available base ($Ph_2P^{\ominus}$ and/or $OH^{\ominus}$) generates bideuteriated 2b Now, as Ph_2PD has become available, deuteriation can occur in the step 3 → 4, leading to trideuteriated 2b The overall result is 2b partially deuteriated at the carbon vacated by the halogen According to this view, it is the irreversibility of the 1→ 3 step that determines the C-7 regiospecifity for these reactions.[5]

Financial support by both C.N R and M.P.I , Roma, is gratefully acknowledged.

FOOTNOTES

§ Freshly sublimed. Stored material, even in the cold, gave poorer yields

† Freshly distilled from lithium aluminum hydride

◊ Prepared by the addition of one molar equivalent of n-butyl lithium to Ph_2PH

† Satisfactory elemental analyses were obtained.

‡ Yields of 2 varied somewhat from run to run, under identical experimental conditions The yields reported here represent the mean values from several runs and have actually to be compared with the maximum theoretical yield for 2 which, according to the mechanism at the Scheme, is 50% A lower yield for the reaction of 2-fluoro- vs. 2-chlorotropone has no precedent.[5] Actually, the reverse order of yields was always found for ipso-nucleofilic substitutions of fluorine [5] We believe that the present reaction of 2-fluorotropone is disfavoured with respect to that of the chloro-analogue, because the rate is limited by the elimination of HX from C-7 — C-2.[5] In fact,elimination of HF is expected to be more difficult than elimination of HCl

‡ δ is given in ppm with respect to internal $SiMe_4$ as reference while J is given in Hz The ^{13}C nmr spectra are fully proton decoupled In the case of 2a the ^{13}C chemical shifts are reported first in a 1 2 $(CD_3)_2CO$-$CDCl_3$ solvent mixture and then in C_6D_6, followed by the differential shift (Δδ) and, within parenthesis, by the multiplicity and the coupling constants of ^{13}C to ^{31}P in the two solvent media, is the order given above

¤ The extent of deuteriation at C-7 varied from run to run, under the same experimental conditions A higher deuteriation extent at C-7 when starting from 1d than 1b may well reflect other, contingent causes than the presence of fluorine in the place of chlorine,as will be apparent from the ensuing discussion in the text.

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A NEUTRAL, ISOLABLE COVALENT ADDUCT BETWEEN PIPERIDINE AND A TROPONOIDAL PHOSPHONIUM SALT

A PECULIAR ACYLPHOSPHORANE

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Summary The phosphonium salt obtained by P-methylation of 2-diphenylphosphinotropone with methyl iodide was found to undergo C-7 addition by piperidine, and loss of hydrogen iodide, to give an acylphosphorane which could be isolated, the regiospecificity of piperidine addition was proven by deuterium labeling at the troponoid ring

In our search for novel σ-adducts between troponoids and bases,[1] tropones bearing either a quaternary ammonium[2] or a sulphonium[3] substituent at C-2 gave particularly interesting results We now report on the reaction of a related phosphonium salt with piperidine, leading to a peculiar acylphosphorane

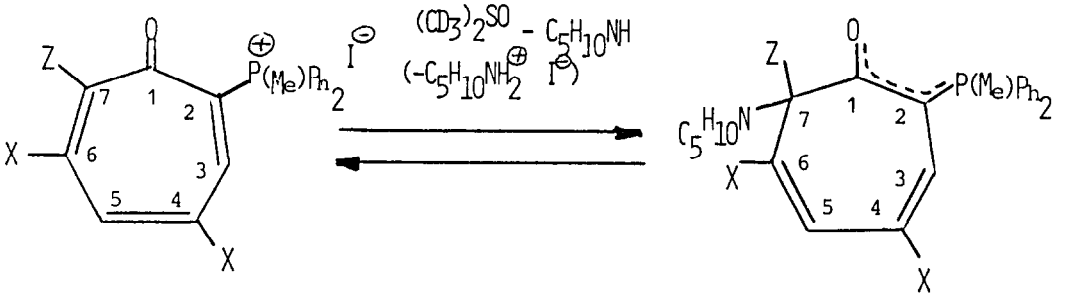
The reactions of either 2-iodo- or 2-chlorotropone with triphenylphosphine or tri-n-butylphosphine, in a variety of solvents, under nitrogen, only led to untractable tars However, when 2-diphenylphosphinotropone[4] (0 2 g, 0 7 mmol) in dry ethyl ether (10 ml), under nitrogen, was added of methyl iodide (0.215 g, 1 5 mmol), an orange-brown powder immediately precipitated, which proved to be the desired quaternary phosphonium salt 1a† (0 28 g, 97 %) Mp 98-101°C, uv, $\lambda_{max}^{(CH_3)_2SO}$ 335, 311, 295 nm, ^{1}H nmr, δ‡ ($(CD_3)_2SO$) 8-7 (15H,m), 3 0 (3H, d, ^2J(PCH) = 13 8 Hz, CH_3), ^{13}C nmr, §δ‡ ($(CD_3)_2SO$) 184 8 (d, ^3J(PCC) = 6.0 Hz, C = O), 120 8 (d, ^1J(PC) = 89.6 Hz, C-2), 8 9 (d, ^1J(PC) = 57 4, CH_3), while the signals for the other carbons were difficult to assign

1b† Was prepared analogously, in a comparable yield, from 2-diphenylphosphino [4,6-$^2H_2$]tropone[4] ^{1}H nmr, δ‡ ($(CD_3)_2SO$) 8-7 (13H, m), 3.0 (3H, d, ^2J(PCH) = 13.8 Hz, CH_3)

On addition of a few drops of piperidine to a ca 0 32 M solution of 1a in dry $(CD_3)_2SO$, under nitrogen, both the ^{1}H nmr signals and the uv absorption bands due to 1a immediately disappeared while the colour of the mixture turned to deep-green and the following signals attributable to the acylphosphorane 2a (Scheme) appeared Uv, $\lambda_{max}^{(CH_3)_2SO}$ 312 nm, ^{1}H nmr, δ‡ ($(CD_3)_2SO$) 7 6 (10H, m, phenyl protons), 6 1 (1H, m, $J_{5,6}$ = 9.0 Hz, ^5J(PCCCCH)= 1 5 Hz, H-5), 5 7 (2H, m, in which a doublet with ^3J(PCCH) = 11 7 Hz could be seen, H-3 and H-4), 5 1 (1H, dd, $J_{6,5}$ = 9 0 Hz and $J_{6,7}$ = 6 0 Hz, H-6), 2 6 (3H, d, ^2J(PCH)= 14.0 Hz, CH_3), ^{13}C nmr, §δ‡ ($(CD_3)_2SO$) 177.5 (d, ^3J(PCC) = 6 0 Hz, C = O), 133

and 129 (series of signals for o-, m-, and p-C of the phenyl groups), 126 7 (s, C-5), 125 4 (d, ^{1}J(PC) = 15 0 Hz, possibly phenyl C-P), 118.6 (s, C-6), 115 8 (d, ^{3}J(PCCC) = 16.4 Hz, C-4), 77 7 (d, ^{1}J(PC) = 104 5 Hz, C-2), 74 9 (d, ^{2}J(PCC) = 10 4 Hz, C-3), 53 3 (s, C-7), 10 4 (d, ^{1}J(PC) = 62 9, CH_3)

SCHEME



1a X = Z = H

1b X = D (and partial deuteriation at C-7)

2a X = Z = H

2b X = D (and partial deuteriation at C-7)

Addition of piperidine, following the above lines, to a sample of 1b obtained from 2-chloro-[4,6-$^{2}H_2$]tropone, partially (ca 20%) deuteriated at C-7, [4] gave 2b. Consistently with the presence of a deuterium at both C-6 and C-4 in 2b, no ^{1}H nmr signal appeared at δ 5 1 and a simple doublet, with ^{3}J(PCCH) = 11 7 Hz, appeared at δ 5 7, while all other ^{1}H nmr signals were quite similar to those reported for 2a Furthermore, in accordance with such a deuteriation pattern, the ^{13}C nmr spectrum for 2b revealed only extremely weak, broadened signals at both δ 118 6 and 115.8, whereas all other ^{13}C nmr signals were similar to those reported for 2a

The structural assignement was further confirmed by isolating both 2a and 2b and by running their ^{1}H nmr spectra in hexadeuteriobenzene in the absence of free piperidine in excess. This allowed us to identify the signals for both H-7 and the bound-piperidine protons which were buried by the signals due to the free-piperidine protons in the spectra reported above for 2a and 2b Thus, always working under nitrogen, a solution of 2a in $(CD_3)_2SO$ was added of chloroform, washed with water, and the green-coloured organic layer was separated, dried over sodium sulphate, and evaporated at reduced pressure By taking great care of always having free piperidine present in traces (which was ensured by adding piperidine during the work-up), dark-green, solid 2a could be isolated ^{1}H nmr, δ (C6D6) 7 0 (10H, m, phenyl protons), 6 4 (1H, m, $J_{5,6}$ = 9 3 Hz, ^{5}J(PCCCCH) = 1.5

Hz, H-5), 5 9 (2H, m, in which a doublet with ^{3}J(PCCH) = 12.0 Hz could be seen, H-3 and H-4), 5 7 (1H, dd, $J_{6,5}$ = 9 3 Hz and $J_{6,7}$ = 6.0 Hz, H-6), 3 4 (1H, d, $J_{7,6}$ = 6 0 Hz, H-7), 3 0 (4H, m, N-CH_2-), 2.0 (3H, d, ^{2}J(PCH) = 13.5 Hz, CH_3), 1.4 (6H, CH_2)

Similar experiments were carried out with 2b In comparison with the ^{1}H nmr spectrum of 2a, the ^{1}H nmr spectrum of 2b in C_6D_6 lacked the δ 5 77 signal, while the signals at δ 6 4, δ 5 9, and δ 3 4 became, respectively, a doublet with ^{5}J(PCCCCH) = 1 5 Hz, a doublet with ^{3}J(PCCH) = 12 0 Hz, and a singlet All other signals were quite similar to those reported above for 2a Clearly this is in full accordance with the deuteriation pattern proposed for 2b.

It is interesting now to consider the peculiar phosphorane 2 in the perpective of the long, continuing debate about the electronic structure of phosphoranes To this concern, we have found that on going from 1a to 2a in $(CD_3)_2SO$ there is a high-field shift of the ^{31}P resonance by 9 6 ppm, which indicates less positive charge at phosphorus with 2a than with 1a This observation, together with the facts that on going from 1a to 2a there is both a high-field shift of the ^{13}C-2 resonance and an increase in the P — C-2 coupling constant, point to an extended conjugation from oxygen to phosphorus, as indicated by 2 in the Scheme This is in qualitative agreement with the conclusions drawn for typical phosphoranes and acylphosphoranes from both spectral data[5a] and calculations[5b,◊]

We thank both C N R and M P I , Roma, for financial support

FOOTNOTES

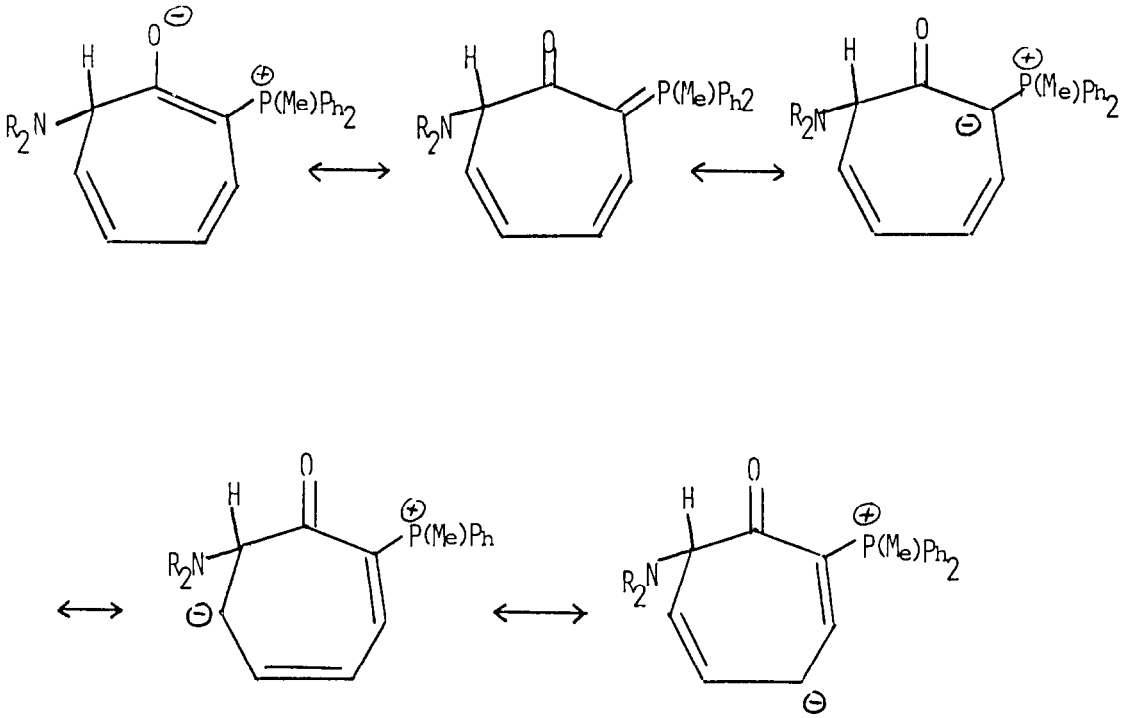
† Satisfactory elemental analyses were obtained

‡ In ppm, with respect to internal $SiMe_4$ as reference (100 MHz for ^{1}H and 25 MHz for ^{13}C).

§ Fully proton decoupled spectrum.

✧ Neither broadening nor weakening of the C-7 signal could be appreciated, which is compatible with the low extent of deuteriation at this carbon (see also the accompanying paper[4])

◊ Unfortunately, since with both 1a and 1b most nmr signals were superimposed with one another, we do not have indications about the extent of the shielding for corresponding hydrogens and carbons, on going from 1 to 2 Therefore, we lack informations about the extent of negative charge dispersal on the seven-membered ring with 2 In view of previous experience with related compounds,[1] it might well be, however, that the entire seven-membered ring enters the conjugation, as is shown by the following canonical forms for 2a



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A NEW GENERAL METHOD OF α-AMIDO-ALKYLATION

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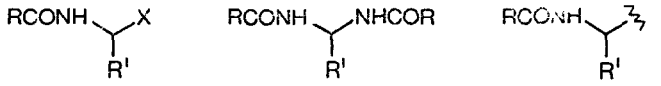
Summary : N-(1-p-Toluenesulphonyl-alkyl) amides, which are readily prepared from an aldehyde, an amide and sodium p-toluenesulphinate, are versatile α-amido-alkylating agents for sulphur nitrogen and carbon nucleophiles.

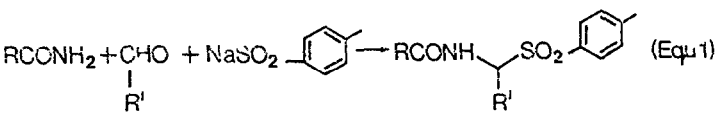
Compounds of type (1, R'=H, X=halogen, -OH, -OR" , -OCOR" , -NHCOR" , $-NR_2$" or $-NR_3$"+) are members of a well known, synthetically important class of α-carboxamido-methylating agents[1].



(1) (2) (3)

Attempted extension of this class of synthon to the preparation of α-carboxamido-alkylating agents (1, R'≠H) fails in all but a few exceptional cases, being restricted almost exclusively to the use of N,N'-alkylidine and N,N'-arylidine-bisamides (2, R'=alk and R'=aryl respectively). We now report the synthesis of a series of sulphones (4), in which the groups R and R' can be aryl, alkyl and substituted alkyl and their use in the α-carboxamido-alkylation of thiols, amines and carbon nucleophiles. The sulphones (4) are therefore electrophilic synthons for the α-carboxamido alkyl moiety (3) and their ready synthesis fills a gap in present synthetic methodology.

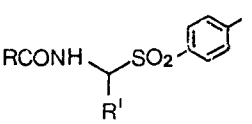
The sulphones (4) are prepared[2] by condensation of an amide, an aldehyde and sodium p-toluene sulphinate in the presence of formic acid, and are stable crystalline solids (eq 1).



(4) (Equ1)

Table 1 lists the sulphones prepared[4], generally we find that aliphatic amides condense more slowly than benzamide, presumably due to the less nucleophilic amide nitrogen atom.

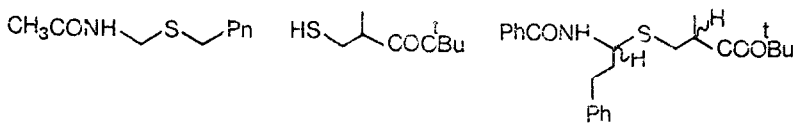
TABLE 1



R =	Ph	Ph	$PhCH_2$	Ph	Ph	CH_3	CH_3
R' =	$PhCH_2$	$PhCH_2CH_2$	$PhCH_2$	CH_3CH_2	Ph	$PhCH_2$	$(CH_3)_2CH$
% Yield	29	60	21	54	40	20	21

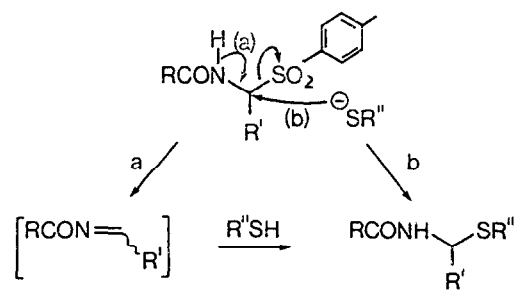
(Yields are not optimised)

These sulphones are versatile α-amido-alkylating agents, reacting readily with sulphur, nitrogen and carbon nucleophiles to give the corresponding α-amido-alkylated products. N-p-Toluenesulphonylmethyl acetamide (4,R=CH_3,R'=H) reacts with benzyl thiol in the presence of potassium t-butoxide to give the thio-ether (5)[5]. In connection with other work we wished to extend this reaction to functionalised thiols. However, under these conditions t-butyl 3-mercapto-isobutyrate (6) failed to react with N(1-p-toluenesulphonyl-3-phenyl-propyl)-benzamide (4,R=Ph,R'=$(CH_2)_2$Ph) to give the expected thio-ether (7) because the potassium salt of the thiol (6) is unstable and decomposes before sulphinate displacement occurs.



(5) (6) (7)

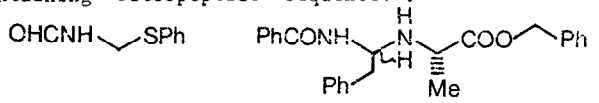
We have investigated the use of alternative bases and find that while triethylamine fails to give significant amounts of the product (7),the use of the more powerful base tetramethyl-guanidine (pKa 13.4) gives (7)[12] as a mixture of diastereoisomers in 96% yield.
Using the other adducts (Table 1) a range of thio-ethers[13] (9) can be prepared in high yield. Two possible alternative mechanisms to account for the formation of thio-ethers of type (9) are, (a) an elimination of toluene sulphinic acid, to give an acylimine intermediate (8), which is trapped by thiol to give the observed product and, (b) a direct S_N2 sulphinate displacement.



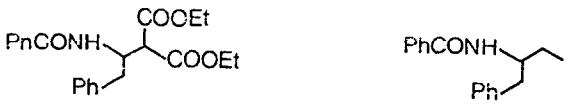
(8) (9)

We have not investigated which of these two mechanisms is operating. However, the following observations are relevant. The sulphinate group of N-p-toluenesulphonylmethyl formamide can be displaced by thiophenol in the presence of weak bases such as triethylamine[6] to give thio ether (10). However alkyl thiols, such as benzyl thiol and (6), require strong bases such as potassium t-butoxide or tetramethylguanidine to initiate reaction. Thus the acidity of the thiol governs the base required a d this suggests that formation of the thiolate anion is required for reaction to occur. Provided that attack on the acylimine (8) is not rate determining these observations favour mechanism (b) under these conditions, because the base required to initiate mechanism (a) would be independent of the thiol used.
The reaction can be extended to other nucleophiles. Thus primary amines, like S-alanine benzyl ester react with N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (4, R=Ph,R'=CH_2Ph) in the presence of tetramethylguanidine to give the acyl aminals (11), as an easily separable mixture of diastereoisomers[7] (71% yield) and represents an efficient method of preparing

peptides containing "retropeptide" sequences[8].



(10) (11)



(12) (13)

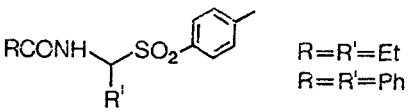
Carbon nucleophiles can also be readily α-amido-alkylated. Reaction of N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (4,R=Ph, R'=CH_2Ph) with diethylmalonate in the presence of sodium hydride in tetrahydrofuran gives the racemic substituted malonate (12)[9] in 78% yield and treatment with ethyl magnesium bromide (solvent THF) gives[10] the benzamide (13)[11, 4] (51%) Thus the sulphones (4), which are readily prepared from an aldehyde, amide and sodium p-toluene sulphinate, are versatile α-amido-alkylating agents for sulphur, nitrogen and carbon nucleophiles.

A typical sulphone preparation is as follows - Freshly distilled phenylacetaldehyde (104g), benzamide (96.8g) and sodium p-toluene sulphinate (171.2g) were dissolved in a mixture of water (2l) and formic acid (200ml) in an inert atmosphere of argon. The mixture was refluxed for 2 hours and the yellow crystalline solid isolated by filtration. Recrystallisation from methanol/chloroform gave the product N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (87g) as a white crystalline solid m.p. 150-2°.

In a typical thioether preparation N-(1-p-toluenesulphonyl-3-phenylpropyl)-benzamide (0.39g) was dissolved in methylene dichloride (5ml) and the thiol (6) (0.2ml) and tetramethylguanidine (0.5ml) added. The reaction mixture was stirred for 2 hours. The product (7) was isolated by pouring the reaction mixture into methylene dichloride (50ml) washing with water, drying over sodium sulphate and evaporating to dryness to give the product (7), which was essentially pure by thin layer chromatography, as an oil (0.39g).

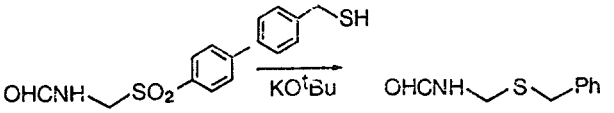
References

1. H.E. Zaugg and W.B. Martin, Organic Reactions, 1965, 14, 52.
2. The experimental method used s a modification of that used by Olijnsma[3] who reported the preparation of (14).



(14)

3. T. Olijnsma, J.B.F.N. Engberts and J. Strating, Recueil, 1967, 86, 463.
4. All new compounds give satisfactory analysis and n.m.r. spectra.
5. We thank Prof.A.M. VanLeusen, Groningen, for communicating the experimental conditions used in the preparation of the formyl derivative (15) prior to publication.



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6. T. Olijnsma, J.B.F.N. Engberts and J. Stratıng, Recueıl, 1972, 91, 209.

7. Dıastereoısomer 1, $C_{25}H_{26}N_2O_3$. Theory, C, 74.7; H, 6.5, N, 7.0, Found, C,75.1; H, 6.5;N, 6.5,n.m.r. ın deuterıochloroform, 1.2δ, 3H, d, J=9 Hz., $\underline{CH_3}$ CH , 2.2δ, 1H, s, NH, exchangeable wıth D_2O; 3.0δ, 2H, d, J=5Hz.,$Ph\underline{CH_2}CH$; 3.5δ 1H, q, J=9Hz., $CH_3\underline{CH}$, 4.8δ, 2H, q, J=15Hz., $Ph\underline{CH_2}O$; 5.2δ, 1H, m, CONHCHNH, 6.3δ, 1H, d, J=10Hz., CONH, 7.1-7.8δ, 15H, m, aromatıc protons. Dıastereoısomer 2,n.m.r. ın deuterıochloroform 1.25δ, 3H, d, J=9Hz., $\underline{CH_3}$ CH ; 2.2δ, 1H, s, NH, exchangeable wıth D_2O; 3.0δ, 2H, m, $Ph\underline{CH_2}CH$; 3.6δ, 1H q, J=9Hz., $CH_3\underline{CH}$; 5.05δ, 2H, s, $Ph\underline{CH_2}O$; 5.2δ, 1H, m, CONH-CH-NH; 6.3δ, 1H, d, J=10Hz., CONH; 7.1-7.8δ, 15H, m, aromatıc protons.

8. M. Chorev, C.G. Wılson and M. Goodman, J.A.C.S., 1977, 99, 8075.

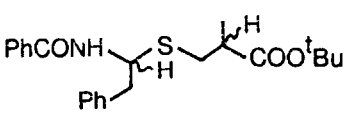
9. $C_{22}H_{25}NO_5$, m.p., 137-8° Theory; C, 68.9, H, 6.5; N, 3.6: Found, C, 68.9; H, 6.5; N, 3.4. n.m.r. ın deuterıochloroform; 1.25δ, 6H, quıntet (2 overlappıng t), $CH_2\underline{CH_3}$, 3.0δ, 2H, d quartet, J_{AB}=14Hz., J_{AX}=10Hz,J_{BX}=8Hz,$Ph\underline{CH_2}$;3.6δ,1H, d, J=4Hz.$(EtOOC)_2\underline{CH}$, 4.2δ,4H,sextet (2 overlappıng quartets), $\underline{CH}2CH3$; 5.1δ, 1H, m, $PhCH_3\underline{CH}$, 7.2-7.9δ, 11H, m, aromatıc protons and CONH.

10. Treatment of 4-phenylsulphonylazetıdın-2-one wıth ethyl magnesıum bromıde gıves 4-ethyl-azetıdın-2-one. T.Kobayash, N. Ishıda and T Hıraoka, J.C.S. Chem. Comm. 1980, 736.

11. N.m.r. ın deuterıochloroform; 0.9δ, 3H, t, $CH_2\underline{CH_3}$; 1.5δ, 2H,sextet, $\underline{CH_2}CH_3$, 2.8δ, 2H, d, J=8Hz., $Ph\underline{CH_2}$; 4.3δ,1H, m, CONH-CH ; 5.9δ, 1H, bd, CONH, 7.1-7.8δ, 10H, m, aromatıc protons.

12. N.m.r. ın deuterıochloroform, 1.2δ, 3H, m, $\underline{CH_3}CH$; 1.4δ, 9H, s, $C(\underline{CH_3})_3$; 2.1δ, 2H, m, $-\underline{CH_2}CH_2Ph$; 2.8δ, 5H, m, $-S\underline{CH_2}-$, $Ph\underline{CH_2}-$, $CH_3\underline{CH}$; 5.5δ, 1H, m, -NHCH ; 6.4δ, 1H, m, -CONH-; 7.2-7.8δ, 10H, m, aromatıc protons.

13. The use of sulphone (4, R=Ph, R'=CH_2Ph) gıves the mıxed dıastereoısomers (16) whıch are thıomethylenepeptıdes[14] of BzPheAlaO^tBu, ın whıch the peptıde lınkage (-CONH-) has been replaced by a thıoether methylene lınkage (-S-CH_2-)[15]



(16)

14. In methylenethıopeptıdes the peptıde lınkage (-CONH-) ıs replaced by a methylene thıo-ether lınkage (-CH_2S-). J.A. Yankeelov, K-F Fok and D.J. Carothers, J.O.C., 1978, 43, 1623, A.F. Spatola and A.L. Bettag, J.O.C., 1981, 46, 2393.

15. For further work see J. Morton, N Renshaw and E.R.H. Walker ın press.

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METHODS FOR THE HOMOLOGATION OF BENZOFURANCARBOXYLIC ACIDS USING DIANIONIC INTERMEDIATES

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Summary: Dianions (2), (5), and (10), can be derived from the corresponding benzofurancarboxylic acids using lithium diisopropylamide, and are useful intermediates for the homologation of the parent acids.

The benzofuran nucleus occurs in a diverse range of natural products. Some of these compounds together with many synthetic benzofurans have significant pharmocological activities.[1] We report herein new methods for the homologation of various benzofurancarboxylic acids based on the intermediacy of dianionic species, derived from the parent acids by metallation using lithium diisopropylamide (LDA).

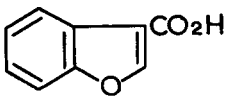
In common with many heterocycles,[2] benzofuran itself undergoes direct metallation at the carbon α to the heteroatom, when treated with n-butyllithium[2] or LDA[3], to give 2-lithiobenzofuran. This useful intermediate can also be obtained from 2-bromobenzofuran by halogen-lithium exchange with n-BuLi.[4,5] It was therefore anticipated[6] that 3-benzofurancarboxylic acid (1)[7] could give rise to dianion (2) on treatment with two equivalents of a strong base. In the event, reaction between (1) and 2.1 equivalents of LDA in tetrahydrofuran (THF) at -78° for 0.5 h., gave an orange solution which was instantly decolourised on addition of chlorotrimethylsilane. Acidic work-up then gave the 2-trimethylsilyl derivative (3a) in virtually quantitative yield. The material was pure according to its ^{1}H n.m.r. spectrum; subsequent crystallisation gave analytically pure (3a) in ca. 80% yield.[8] Similar reactions with benzaldehyde and heptanal were slower, but after allowing the reaction mixture to warm to room temperature, (3b) and (3c) respectively were obtained in ca. 75% isolated yield. Unfortunately, attempted alkylations of (2) with ethyl iodide failed to give more than traces of (3d) under a variety of conditions. Alkylations of dianions related to (2) have also been found to be unsatisfactory.[6] On warming, the dianion (2) was slowly protonated (THF as proton source?); for example, when a solution of (2) was allowed to reach 0°C during 0.5 h., then quenched with Me_3SiCl, only a 35% conversion to (3a) occurred, the remainder of the product being starting

material (1).

We have also investigated the possibility of utilising this method for the homologation of benzofuran-2-carboxylic acid (4a).[9] Dean et.al.[3] have reported that (4a), on treatment with 2 equivalents of LDA followed by CO_2, gave a good yield of benzofuran-2,3-dicarboxylic acid together with some of the acetylenic acid (6a), arising from ring opening of the intermediate dianion (5a). We have been unable to extend the utility of this reaction; attempts to trap dianion (5a) with a variety of electrophiles (Me_3SiCl, MeI, RCHO) all failed to give more than traces of the desired products, even when the reactions were carried out at low temperatures (< -90°C). In all cases, the major or exclusive product was the acetylenic acid (6a).[4,5] Indeed, treatment of a benzofuran-2-carboxylic acid with 2.1 equivalents of LDA at -78°C, followed by warming to room temperature is, in our opinion, an effective method for the preparation of (2-hydroxyphenyl)propynoic acids (6)!

By contrast, metallation of 5-methoxybenzofuran-2-carboxylic acid (4b)[9] using LDA at -90°C followed by the addition of methyl iodide, benzaldehyde, or n-heptanal gave the desired products, (7a), (7b), and (7c) respectively, in ca. 90% yield accompanied by, at most, only traces of the ring opened product (6b). Presumably, the "para" methoxy group stabilises the intermediate dianion (5b), with respect to ring opening, by causing the furan oxygen to be a poorer leaving group than in the unsubstituted dianion (5a). Similarly, dianion (5d), in which the methoxy substituent is ortho to the furan oxygen, could also be trapped by the same electrophiles at -90°C to give (8a), (8b), and (8c). In these cases, the stabilising effect was not so great and the ring-opened product (6d) was present to an extent of ca. 20% in the isolated products. Nevertheless, the desired products (8a-c) could be obtained in 50-60% yield after chromatography. In line with these observations, the 6-methoxy acid (4c),[9] in which the methoxy group is meta to the furan oxygen, underwent rapid ring opening at -90°C to give only the acetylenic acid (6c).

In an attempt to circumvent the problem of ring opening in benzofuran-2-carboxylic acid (4a), we investigated the possibility of forming a dianionic species (10)[10], from 3-methylbenzofuran-2-carboxylic acid (9)[11]. We were pleased to find that the bright-red dianion (10) could indeed be obtained and that it coupled with a range of electrophiles to give the desired products (11a-e) in ca. 90% isolated yields. We have found that these reactions are best carried out using 2.1 equivalents of LDA in THF at -10°C. In contrast to the vinyl carbanions (vide supra), dianion (10) also reacted very efficiently with ethyl iodide, to give (11g) in 80% yield, and with 1,2-epoxybutane to give (11f) in 93% yield. Thus, this method appears to have considerable potential for the efficient synthesis of many 3-substituted benzofuran-2-carboxylic acids.



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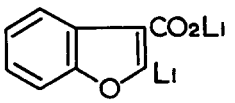

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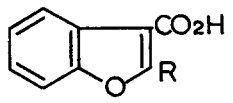


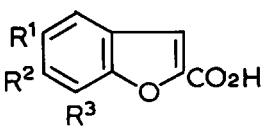
(3)

(a) R=SiMe$_3$

(b) R=CH(OH)Ph

(c) R=CH(OH)n-hex

(d) R=Et



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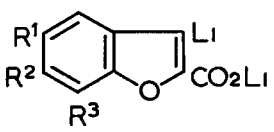

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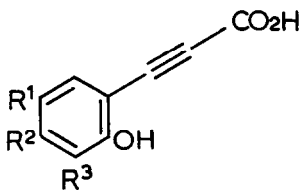
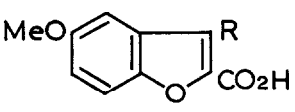


(6)

(a) $R^1=R^2=R^3=H$; (b) $R^1=OMe$; $R^2=R^3=H$; (c) $R^1=R^3=H$; $R^2=OMe$;

(d) $R^1=R^2=H$; $R^3=OMe$.

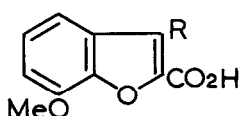


(7)

(a) R=Me

(b) R=CH(OH)Ph

(c) R=CH(OH)n-hex



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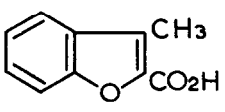

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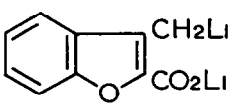

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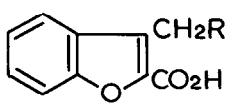

(11)

(a) R=Me

(b) R=SiMe$_3$

(c) R=CH(OH)Ph

(d) R=C Me$_2$(OH)Ph

(e) R=CH(OH)n-hex

(f) R=CH$_2$CH(OH)Et

(g) R=Et

Acknowledgements

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AN EFFICIENT SYNTHESIS† OF HEXA-SUBSTITUTED BENZENES AND THE DISCOVERY OF A NOVEL HOST CONFORMATION FOR HEXAKIS(β-NAPHTHYLTHIO)BENZENE

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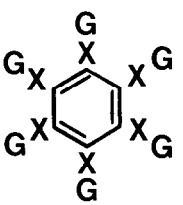
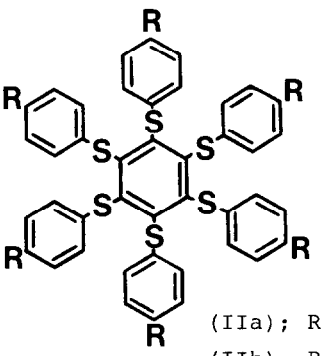
Summary. The title host molecule (III) has been synthesised by reaction of hexachlorobenzene with an excess of the sodium salt of β-mercaptonaphthalene in 1,3-dimethyl-2-imidazolidinone (DMEU) as solvent; other hexakis(arylthio)-benzenes, hexakis(phenoxy)benzene (IV), and hexakis(phenylseleno)benzene (V) were prepared analogously from hexahalobenzenes, HMPA being used as solvent in the last case. An X-ray analysis of the channel-type adduct of (III) with 1,4-dioxan as guest reveals a unique host conformation in which the side-chains are not situated alternately above and below the plane of the central benzene ring.

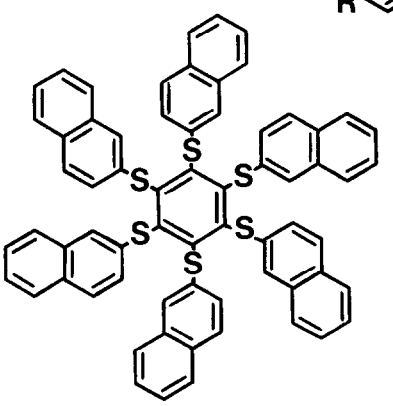
Although considerable attention has been focused on the study of hexa-host[1] molecules with a two or more atom link X joining the outer rings (G) to the central benzene ring, general formula (I), the important one-atom class has



(I)

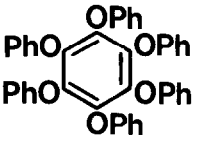


(IIa); R = H
(IIb); R = Me
(IIc); R = t-Bu

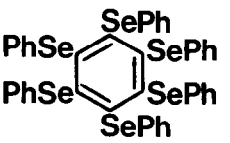


(III)

† Information protected by U.K. Patent application no. 8217510.



(IV)



(V)

been comparatively neglected due to synthetic difficulties.[2] This latter class is of particular interest owing to its close formal resemblance to the (OH...O) hydrogen-bonded hexameric unit found in the clathrates of phenol, hydroquinone, Dianin's compound and related systems.[5] Greatly encouraged by a recent report[6] by Tiecco and colleagues of complete substitution of C_6F_6 and C_6Cl_6 by i-PrSNa in HMPA, to give $C_6(SPr^i)_6$ in high yields, we investigated the action of the arenethiolate salt PhSNa on C_6Cl_6 and found remarkably facile displacement of all the chlorine atoms giving, after appropriate work-up, a 90% yield of pure $C_6(SPh)_6$, (IIa), entry 5 in Table. The first example of a hexakis(arylseleno)-benzene was prepared analogously, reaction of PhSeNa with C_6Cl_6 (Table, entry 6) furnishing a 51% yield of hexakis(phenylseleno)benzene (V), which on recrystallisation from pentachloroethane containing excess CBr_4, gave the CBr_4 adduct of (V) as beautiful orange rhombs, m.p. 195-196°C, (after apparent guest loss at ca. 100°C), a host/guest ratio of 1:2 being determined by microanalysis for halogen.[7]

Wishing to avoid prolonged use of the known[8] carcinogen HMPA, we sought an alternative solvent capable of promoting efficient aromatic halogen displacement. 1,3-Dimethyl-2-imidazolidinone, dimethylethyleneurea (DMEU), was found to be a remarkably effective, and probably much less toxic, substitute.[9] Reaction of C_6F_6, C_6Cl_6, or C_6Br_6 with PhSNa in DMEU gave in each case a high yield pure (IIa), entries 2-4 in Table; and the general nature of this substitution procedure is suggested by the analogous high yield synthesis, employing the sodium salt of the appropriate arenethiol, of hexakis(p-t-butylphenylthio)benzene (IIc), entry 7, and hexakis(β-naphthylthio)benzene (III), entry 1. The unique host molecule conformation of (III) in its 1,4-dioxan adduct is described below. To our knowledge no hexakis(aryloxy)benzene has yet been reported and hexakis-(phenyloxy)benzene (IV), an analogue of the hydrogen-bonded hexameric unit present in phenol clathrates,[10] appeared an attractive target. This hexaether, whose potential inclusion properties are currently being studied, was obtained as colourless needles, m.p. 277-280°C (with sublimation); in this case instead of the normal ambient conditions a temperature of 120°C was employed to effect complete substitution.

TABLE Conditions for complete substitution of hexahalobenzenes

Entry No	Product[c]	Solvent	Substrate, molar equivalents ArXNa	Time,[a] temperature	Yield[b]	m p.
1	(III)	DMEU	C_6Cl_6, 12	5d, ambient	72%	194.5-195°C
2	(IIa)	DMEU	C_6F_6, 12	2d, ambient	86%	186.5-187°C (lit.[4] 186-186 5°C)
3	(IIa)	DMEU	C_6Cl_6, 12	3d, ambient	96%	
4	(IIa)	DMEU	C_6Br_6, 12	2d, ambient	90%	
5	(IIa)	HMPA	C_6Cl_6, 12	4d, ambient	90%	
6	(V)	HMPA	C_6Cl_6, 12	4d, ambient	51%	195-196°C
7	(IIc)	DMEU	C_6Cl_6, 12	3d, ambient	76%	242-243.5°C
8	(IV)	DMEU	C_6F_6, 18	4d, 120°C	73%	277-280°C

a The minimum times required have not yet been established.
b. The yields are not optimised.
c. All new compounds gave a satisfactory microanalysis and had spectroscopic properties (i.r., ^{1}H n.m.r., and m.s.) concordant with their formulated structures.

Crystal structure of compound (III).‡

The host (III) forms a highly crystalline adduct with 1,4-dioxan, the host/guest ratio determined by ^{1}H n.m.r. being 1:1. The triclinic crystals have a = 10.118(2), b = 15.172(2), c = 20.379(5) Å, α = 75.05(2), β = 82.64(2), γ = 68.45(1)°, space group $P\bar{1}$, and D_c = 1.32 g cm^{-3} with two host and two guest molecules in the unit cell. A crystal measuring 0.1 x 0.15 x 0.05 mm, enclosed in a thin-walled glass capillary tube, was used for the measurement at 20°C of 9841 independent X-ray intensities (MoK$_\alpha$ radiation) by a θ-ω scan on a Nonius CAD4 diffractometer. The structure was solved by direct methods employing 5100 X-ray intensities with $F^2 > 2\sigma(F^2)$, and refinement by least squares methods gave a final R factor 0.048. During the course of the analysis all the host hydrogen atoms were located and included in subsequent refinement. The guest hydrogen atoms were not located.

Figure 1 shows a stereoview of the host molecule (III), which is located in a general position in the unit cell. In contrast with the trigonal conformation of $C_6(SPh)_6$ which is located on a point of $\bar{3}$ symmetry in its CCl_4 clathrate,[4] (III) is not constrained to have alternate disposition of side chains above and below the plane of the central ring: indeed, instead of having three-fold symmetry the molecule approximates to the point group C_2, adjacent 'legs' being found on the same side of the central ring, with a corresponding adjacent pair on the opposite side. The molecular conformation is reflected in a signif-

‡The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

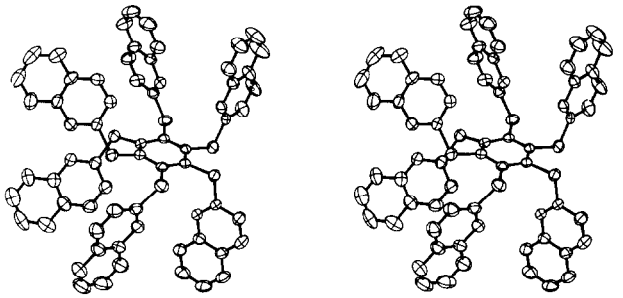


Figure 1. A stereoview showing the host molecule of hexakis-(β-naphthylthio)benzene in its 1,4-dioxan channel-type inclusion compound. All hydrogen atoms have been omitted for clarity. The molecule has approximate $\underline{C}_2$ symmetry.

icant distortion of the central benzene ring, which has an approximate two-fold rotation axis. The retention of inclusion properties for (III), whose conformation corresponds to an interchange of two adjacent 'legs' away from a trigonal situation,[5] is of particular interest in view of the recent consideration by Huang and Mak[11] of the dominant role that two-fold molecular symmetry plays in the architecture of the lattices of many inclusion compounds. Figure 2 shows a

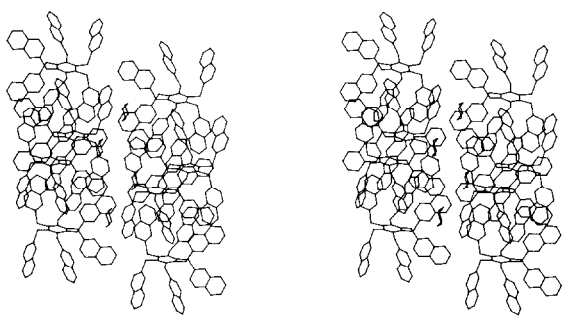


Figure 2. A stereoview showing the host-guest packing of the adduct of (III) with 1,4-dioxan as guest in the triclinic crystal. The chair-shaped 1,4-dioxan molecules can be seen to be located in continuous voids in the structure.

stereoview of the host-guest packing; the host and guest molecules both occupy general positions in the centrosymmetric structure. The 1,4-dioxan guest molecules have a chair conformation and can be seen to be located in continuous voids running through the crystal.

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