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8-PHOSPHABICYCLO[3.2.1]OCTANES—II[1]

THE SYNTHESIS AND STEREOCHEMISTRY OF 8-PHOSPHABICYCLO[3.2.1]OCT-6-ENES

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Abstract—Several new 8-phosphabicyclo[3.2.1]oct-6-enes and -6-en-3-yl acetates were prepared by the alkyl (or aryl)dihalophosphane addition to cyclohepta -1,3-diene and 1-acetoxy cyclohepta-3,5-diene. The P-configuration in two P-epimer pairs (**3**, **4** and **5**, **6**) and three other compounds which were each obtained as a single isomer (**1**, **2** and **7**) was determined by investigation of the NMR spectra, i.e. by complexation of the compounds with $Eu(dpm)_3$ as well as from the various phosphorus-hydrogen coupling constants. Compounds possessing the same P-substituent were correlated among themselves and in the case of the P–Ph bearing compounds (**1** and **7**) further correlation to a known compound (**8a**) was established. The chemical behaviour of the C_6–C_7 double bond is discussed and compared with the corresponding behaviour in trop-6-enes. Great steric hindrance was found for this bond, for which the following sequence is suggested:

$$C\text{-}3\alpha\text{-}H > Ph\text{-}P > Me\text{-}P > O = P.$$

The synthesis of a phosphaatropine analog is described.

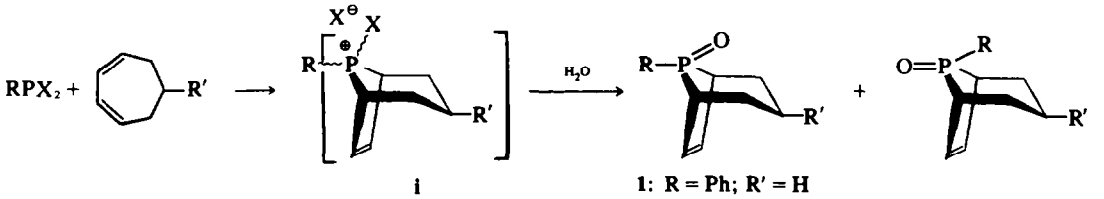
Being interested in the 8 - phosphabicyclo[3.2.1]octane system, several synthetic approaches were tried for its preparation. Actually, it was found that at least three methods could be used for this purpose: (a) the double Michael addition of primary phosphines to cyclohepta - 2,6 - dien - 1 - one[1]; (b) cycloaddition of alkyl or aryldihalophosphanes to cyclohepta - 1,3 - dienes and (c) cycloaddition of oxyallylic cations to suitable phospholes.[2]

In this report the second method is described in detail. Furthermore, as two functional groups could be introduced by this synthesis (at C_6–C_7 and C_3, as compared to C_3 alone in the molecules prepared according to the first synthetic method) the stereochemistry study of this bicyclic system could be further developed.

In the event a whole series of 8-alkyl (or 8-aryl) - 8 - oxo - 8 - phosphabicyclo[3.2.1]oct - 6 - enes and - 6 - en - 3 - yl - acetates were prepared utilizing cyclohepta - 1,3 - diene, or 1 - acetoxycyclohepta - 3,5 - diene respectively as dienes, and trivalent alkyl or aryl dihalophosphanes as dienophiles (Scheme 1).

The majority of the syntheses were carried out simply by allowing a mixture of molar equivalents of the dienes and the dihalophosphanes to stand at ambient, or elevated (80°–100°) temperatues. The results (yield and time of reaction)† as function of temperature, dienophile and performance condition, in solution or neat (Table 1) are in accordance with the expected ones according to the known data for RPX_2 addition to other dienes.[3]

†It is difficult to judge visually when the reaction is complete; as the reaction proceeds, liquid is absorbed by the precipitate.



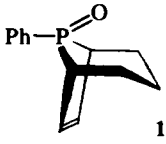
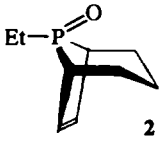
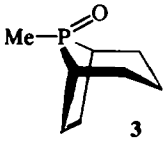
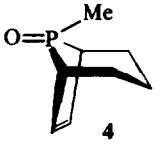
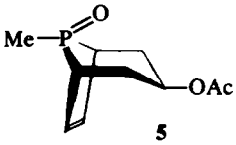
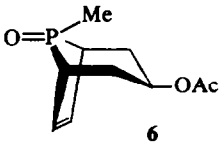
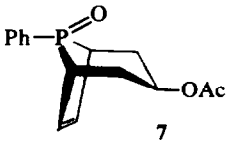
1: R = Ph; X = Cl or Br; R′ = H
2: R = Et; X = Cl; R′ = H
3: R = Me; X = Cl or Br; R′ = H
4: R = Me; X = Cl; R = OAc
5: R = Ph; X = Cl; R′ = OAc

1: R = Ph; R′ = H
2: R = Et; R′ = H
3: R = Me; R′ = H
5: R = Me; R′ = OAc
7: R = Ph; R′ = OAc

4: R = Me; R′ = H
6: R = Me; R′ = OAc

SCHEME 1.

Table 1.

Compound	Conditions	H_2 H_3 H_4 (6H)	$H_1(H_5)$ ($^2J_{PH_{1(5)}}$)	$H_6(H_7)$ ($^3J_{PH_{6(7)}}$)	P–Ph or P–Me	Other protons
 **1**	r.t., 6d, a, 50% r.t., 7m, a,* 32% 85°, 7d, b, 7%	1·46– 2·48m	2·72dm (12 Hz)	6·06dm (20 Hz)	7·36m (3H) 7·68m (2H)	—
 **2**	100°, 14d, a, 35%	0·90– 2·15m	2·40dm (11 Hz)	6·10dm (18 Hz)		0·9–2·15m P–Et(5H)
 **3**	80°, 4d, b, 80% r.t., 3m, b, 60% (3/4, 1:2 to 1:6)	1·10– 2·20m	2·40dm (12 Hz)	6·01dm (18 Hz)	1·48d (J = 14 Hz)	
 **4**	r.t., 5d, a, 90% (3/4, 2:1)	1·50– 1·90m	2·78dm (16 Hz)	6·25dm (18·5 Hz)	1·78d (J = 13 Hz)	
 **5**	r.t., 2m, b,** 35% (5/6, 95:5)	2·00– 2·30m (4H)	2·60dm (12 Hz)	6·18dm (18 Hz)	1·50d (J = 13 Hz)	4·75m (H_3) 2·03s (OAc)
 **6**		†	†	6·25dm (18 Hz)	1·59d (J = 13 Hz)	1·99s (OAc)
 **7**	r.t., 2m, b,** 9%	2·10– 2·50m (4H)	2·88dm (13 Hz)	6·13dm (18 Hz)	7·38 (3H) 7·65 (2H)	4·81m (H_3) 2·03s (OAc)

Conditions: 1. temp; 2. time (d-days, m-months); 3. a-dibromophosphane, b-dichlorophosphane; 4. yield.
*In petrol–ether solution.
**Conditions of dryness were of primary importance.
†No exact value was available as compound **6** was not obtained in a pure state.

The reactivity of the various dihalophosphanes was found to be in the order: $CH_3PBr_2 > PhPBr_2 > CH_3PCl_2 \gg C_2H_5PCl_2 > PhPCl_2$, namely $R(Ar)PBr_2$ reacts faster than $R(Ar)PCl_2$ and RPX_2 faster than $ArPX_2$. Unexpectedly and difficult to explain, was the great gap between the relative reactivities of CH_3PCl_2 and $C_2H_5PCl_2$. Furthermore it was surprising to find that PBr_3† (or PCl_3) did not react with the cyclohepta - 1,3 - diene, while only some decceleration in comparison to CH_3PBr_2 could be expected.[3]

Using a dilute solution of the reactants in an inert

†PBr_3 is known to react with 2,3 - dimethylbutadiene even at −10° to give 85% of the adduct salt after 1 h.[3]

solvent tends to reduce the reaction rate drastically (Table 1, compound **1**).

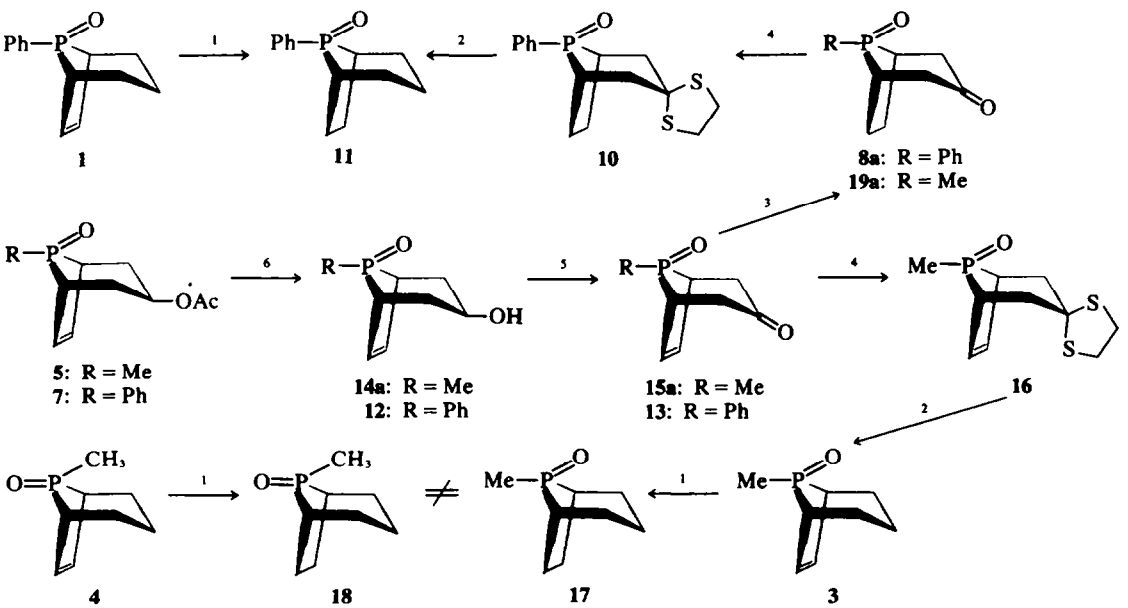
The reactive nature of the adducts (**i**) which precipitated as solids or gums renders them difficult to work with, therefore they were directly converted to the stable phosphine oxides. These oxides similar to other known 1-alkyl (or aryl) - 1 - oxo - 3 - phospholenes[4] were found to be (except for **1**) very hygroscopic.

Of special interest was the number of isomers isolated from the various reaction mixtures. It turned out that in the case of CH_3PX_2 two P-epimers could be isolated (**3**, **4** and **5**, **6**) while using $EtPCl_2$, $PhPCl_2$ or $PhPBr_2$ only a single stereoisomer was obtained (**1**, **2**, and **7** respectively). The hydrolysis mechanism of adducts of type **i**, to give the corresponding phosphine oxides, has already been widely discussed by Quin,[5] and is as yet unconfirmed. Nevertheless, it was worthwhile in this context to see whether the two P-epimers originate from two initially obtained adduct salts, or whether the splitting into two isomers occurs only in the hydrolysis stage. As far as can be determined from the NMR (a poor spectrum is obtained due to the low solubility of **i** in $CDCl_3$) adduct **i** (R=Me, X=Cl) is only one compound, indicating that the splitting into two isomers occurs in the hydrolysis. As there is no unequivocal hydrolysis mechanism the change in the **3** to **4** ratio, starting from $MePCl_2$ in comparison with $MePBr_2$, is uncomprehensible. In contrast to the situation with $MePX_2$, $EtPCl_2$ and $PhPX_2$ gave only one isomer which is not surprising as far as the 8-phenyl group is concerned. It was already found by us that the preferential P-epimer in 8 - oxo - phosphabicyclo [3.2.1]octan - 3 - ones is the one in which the aryl group is equatorial to the phosphorinanone ring (**8a**), being the configuration in which, according to a Dreiding model the phenyl group is furthest away from the cycloheptanone skeleton,[1] all the more so in compound **1**, possessing the C_6–C_7 double bond. An additional proof that **1** is indeed one isomer was derived by its reduction to the corresponding phosphine which was immediately transferred to its methiodide salt (**9**); the NMR spectrum of **9** showed one doublet for the P–CH_3 group, thus confirming the above assumption.

The situation was less clear in the case of $EtPCl_2$, (whose unexpected low reactivity, in comparison to $MePCl_2$, was already mentioned above). Only one isomer (**2**) was obtained, the reason for which is not obvious. There exists the possibility that a possible increment in energy caused by a somewhat restricted rotation around the Et–P bond in the axial isomer should entirely exclude this epimer; however as the understanding of this preference depends on the yet ynknown hydrolysis mechanism the problem remains open. Not surprising was the observation that the reaction of 1 - acetoxycyclohepta - 3,5 - diene gave in all cases only the products with the acetoxy group in the less hindered C - 3β - equatorial position.* The C - 3α - proton appears as a quintet at δ 4·75 (compound **5**), while the C - 3β - proton *vide infra* gives rise to a triplet like signal at δ 4·15 (compound **32**).

The configuration of the phenyl group in compounds **1** and **7** was established by their correlation to compound **8a** as described in scheme-2. The P-configuration of **8a**, as opposed to its P-epimer **8b**, was unequivocally established by X-ray analysis.[6] This configuration has originally been

*We nominate the side of the cycloheptane ring in which the P-atom is located as the β-side and the other one as the α-side.



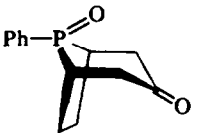
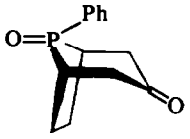
SCHEME 2. 1. H_2 Pd/C; 2. H_2 RaNi; 3. H_2 PtO_2, 4. $(HSCH_2)_2$, BF_3-etherate; 5. Jones reagent; 6. 1% KOH in MeOH.

suggested by us on grounds of the relative chemical shifts of several closely related compounds as well as the use of uranyl nitrate complexation of **8a**, its P-epimer (**8b**) and related compounds in the NMR spectrum.[1] Later, after discovering the many possible applications of lanthanide shift reagents for structure and stereochemistry elucidations, we also showed its usefulness for phosphine oxides complexation in general, and stereochemistry elucidation of these compounds in particular.[7] The P-configuration in compounds like **8a** and **8b** was shown to be unequivocally determined by this method. Although the NMR spectra of such compounds is quite complicated, the relative shifts of the $C_{2(4)}$ in comparison to the $C_{6(7)}$-protons, and particularly if a C_6–C_7 double bond exists, were sufficient for the structure elucidation. Actually the Eu(dpm)$_3$ was assumed to be located in *ca* 3·5 Å from the oxygen of the P=O group[8] (slight variations in this value do not alter the results) and from this point the distances between the Eu-atom and any particular proton (d_i) and the O....Eu....H_i angle (θ_i) were measured for each P-epimer. The calculated F_i values, $F_i = (3\cos^2\theta_i - 1)/d_i^3$ according to the McConell–Robertson equation,[9] for the $C_{2(4)}$ and $C_{6(7)}$ protons (and in some cases for all the skeleton protons) of the P-epimer pairs were then correlated to the measured $\Delta\delta_i$ values ($\Delta\delta_i = \delta$ complexed $- \delta$ uncomplexed for a chosen Eu(dpm)$_3$ to-substrate concentration). The epimer for which a better correlation between the various F_i to $\Delta\delta_i$-values were found was assumed to be the correct one* (for an example see Table 2).† The stereochemistry of compounds **3** and **4** were determined in a similar way; furthermore they were also correlated to compound **5** as shown in scheme-2. The 8 - methyl - 8 - oxo - 8 - phosphabicyclo[3.2.1]oct - 6 - en -3 - one (**15a**) appearing in this correlation scheme was found to be an additional convenient compound for the Eu-complexation; in this case the stereochemistry was obvious immediately, as the two axial $H_{2(4)}$ protons were shifted 4-fold as much as the $C_{6(7)}$ ones (3·0 ppm as compared to 0·70 for an Eu(dpm)$_3$/Substrate ratio of 0·18).

The δ P–Me values of **3** as compared to **4**, and **5** as compared to **6**,‡ were found to be in accordance with the assumed stereochemistry showing the expected[1] diamagnetic anaisotropy effect of the C_6–C_7 double bond on the P–Me group in **3** and **5** (Table 1).

Although in the case of **2** only one isomer exists, the chemical shifts of the identified protons, as well as the almost similar line slopes observed for these protons, in the Eu(dpm)$_3$ complexed NMR spectrum, as compared to that of **3**, indicated the same stereochemistry in the latter. Furthermore, comparison of the $J_{P,H(15)}$-values of the whole series (Table 1) showed that this value can also serve as an additional criterion; being 11–12 Hz for the equatorial P-alkyl (or aryl)epimers and 16 Hz for the axial epimer.

Table 2.

Compound		 **8a**	 **8b**
$H_{2(4)}ax$	d_i	4·7 Å	7·6 Å
	θ	34°	12°
	F	$10{\cdot}4\times10^{-3}$	$4{\cdot}26\times10^{-3}$
	$\Delta\delta$	1·51	1·10
$H_{2(4)}eq$	d_i	6·5	8·1
	θ	35°	14°
	F	$3{\cdot}7\times10^{-3}$	$3{\cdot}19\times10^{-3}$
	$\Delta\delta$	0·60	0·70
$H_{6(7)\alpha}$	d_i	7·8	7·1
	θ	11°	35°
	F	$3{\cdot}98\times10^{-3}$	$3{\cdot}49\times10^{-3}$
	$\Delta\delta$	1·00	0·6
$H_{6(7)\beta}$	d_i	8·0	5·5
	θ	18°	33°
	F	$3{\cdot}35\times10^{-3}$	$6{\cdot}67\times10^{-3}$
	$\Delta\delta$	1·00	1·30

[Eu(dpm)$_3$/Substrate] = 0·25.
$F_i = (3\cos^2\theta_i - 1)/d_i$.[3]

Consideration of the expected stereochemical behaviour of the 8-phosphabicyclic system made us look for an appropriate model compound. Formally the aza analog namely the trop - 6 - ene, is the closest, but it is disqualified for the following conformational reason: the possible N-substituent flip enables easy β-attack on the C_6–C_7 double bond, forthermore it does not exclude the α-attack, as the chair $\rightleftharpoons$ boat equilibria is not essentially prevented, *vide infra.* Actually the 8-substituted carbobicyclo[3.2.1]oct - 6 - ene system had to be the chosen one, but unfortunately the minimal available informative data on it, ruled it out. The existence of the P-atom in our case is expected to raise the energy of the phosphorinanic ring in the boat conformation due to strong flagpole interactions (between C-3β-H and the axial P-substituent) which cannot be released, in this rigid system, by twisting the boat. Thus it was interesting to investigate the influence of the P-substituent§ (alkyl, aryl *versus* phosphoryl groups) which prevents β-approach to the C_6–C_7 double bond attack by electrophilic reagents, as compared to the C - 3α - protons disturbing the α-approach to this bond.

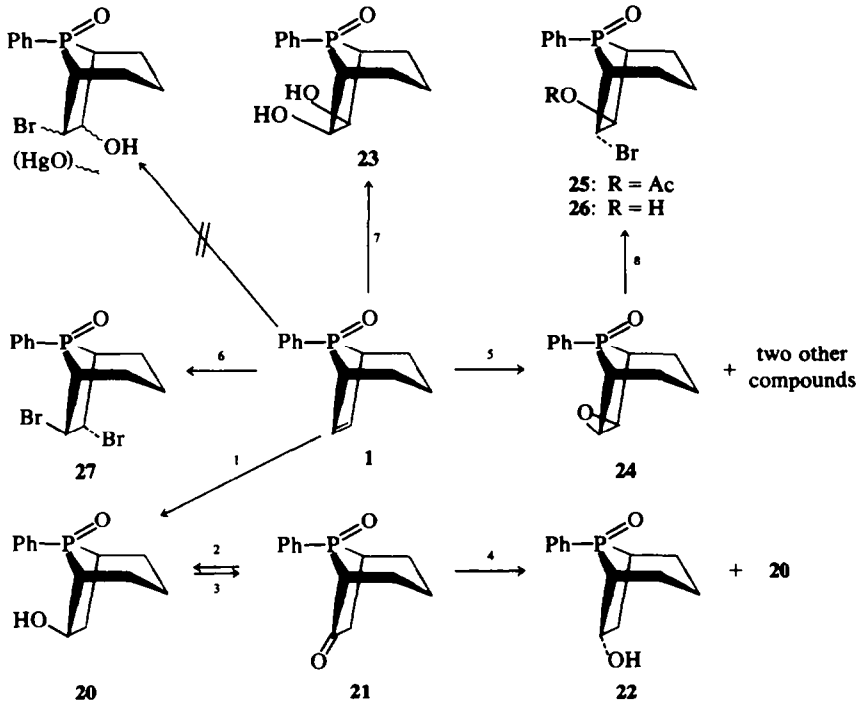
Actually, several reactions were performed on **1** (Scheme-3), hydroboration gave, in good yields, one

*In the case of **8a**, **8b** (Table 2) even the largest $\Delta\delta_i/d_i$ values could distinguish between the isomers due to the small variations in the corresponding angles.

†The correlation between F_i and d_i in Table 2 is good especially for the largest shifts (for H_2(ax) in **8a** and $H_{6\beta}$ in **8b**).

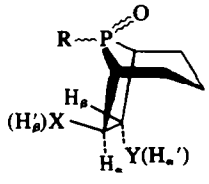
‡Compound **6** could not be isolated pure, but from the NMR of the mixture with **5** the value of the latter could be substracted.

§The influence of the C-7 alkyl group in 7-alkyl norbornenes on the β-attack on the double bond is well known, e.g. in the 7,7 - dimethyl - 2 - norbornene *endo* addition to the double bond becomes important[10] and a similar behaviour can be expected also in our case.



SCHEME 3. 1. B_2H_6; 2. H_2, RaNi; 3. Jones reagent; 4. $NaBH_4$; 5. *m*-chloroperbenzoic acid, Δ; 6. Br_2, Δ; 7. OsO_4; 8. 48% HBr, HOAc.

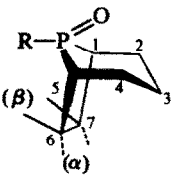
compound (**20**) which, according to the NMR spectrum must possess the hydroxyl in the C - 6β - configuration. The configuration assignment at carbons 6 and 7, the ones involved in this and other herewith described reactions, was estimated according to the $^3J_{PH_{6(or\,7)}}$, $J_{H_5H_6}$, $J_{H_1H_7}$ and $J_{H_6H_7}$ values (Table 3). Considering the measured J-values for this series, the expectation that $^3J_{PH_{6(or\,7)}}$ should be correlated to the $PC,CH_{6(or\,7)}$ angle by a Karplus like equation,[11] and of course existence of the Karplus equation for the $^3J_{HH}$ coupling constants, the following correlations are suggested:



for X = H and Y ≠ H: $^3J_{PH_\beta} = 0(\sim 95°)$; $J_{H_\beta H_\alpha} = 4(\sim 120°)$; $J_{H_\beta H_{\beta'}} = 9(\sim 0°)$ and $J_{H_\beta H_{1(5)}} = 5(\sim 30°)$, and for Y = H and X ≠ H: $^3J_{PH_\alpha} = 28\text{–}29(\sim 150°)$; $J_{H_\alpha H_\beta} = 4(\sim 120°)$; $J_{H_\alpha H_{\alpha'}} = 9(0°)$ and $J_{H_\alpha H_{1(5)}} = 0(\sim 90°)$.

As can be seen from Table-3 and the above summarized data, the $^3J_{PH}$ value, which could be measured in every case by an heterodecoupling experiment, turned out to be most significant for the C_6, C_7 unequivocal configuration estimation. Oxidation of **20** to the corresponding ketone **21** followed by reduction by $NaBH_4$ afforded a mixture of the two possible alcohols **20** and **22** respectively. On the other hand, catalytic hydrogenation of **21** resulted in **20** exclusively. As can be seen below, all the electrophilic reagents approach the C_6–C_7 double bond of **1** from the β-direction, whereas the catalytic reduction of the C-6 ketone of **21** occurs, contrarily from the α-side. Examination of the Dreiding model of **1** can explain this behavior as a result of the relatively large disturbance caused by the P–Ph group as compared to the C-3 methylenic group in the catalytic reduction of the sideways ketone, whereas with the the smaller borohydride anion this preference does not exist. Catalytic reduction of 3α - acetoxytropan - 6 - one gave exclusively the 6α-hydroxyl,[12] most likely due to the possibility of the N-Me group to occupy the axial position (towards the piperidine ring) in the transition state, which is undoubtedly impossible in our case, indicating, as predicated above, the difference between this and our system. Oxidation of **1** with OsO_4 in pyridine occurs also from the β-side to give the *cis*-diol **23**, indeed, in poor yields even after prolonged reaction time (Table-3) bringing to light for the first time, the hindrance to additions to the C_6–C_7 double bond by more bulky reagents. Several attempts which have been made to prepare a bromohydrine as well as the oxymercuration derivative, even under drastic conditions failed. Furthermore, bromination, at r.t. and epoxidation under a whole variety of conditions (perbenzoic acid at r.t., H_2O_2 + Na_2WO_4, peracetic acid),[13] which were successfully carried out on trop - 6 - en - 3 - ol giving the β-epoxide,[13] left compound **1** unchanged.

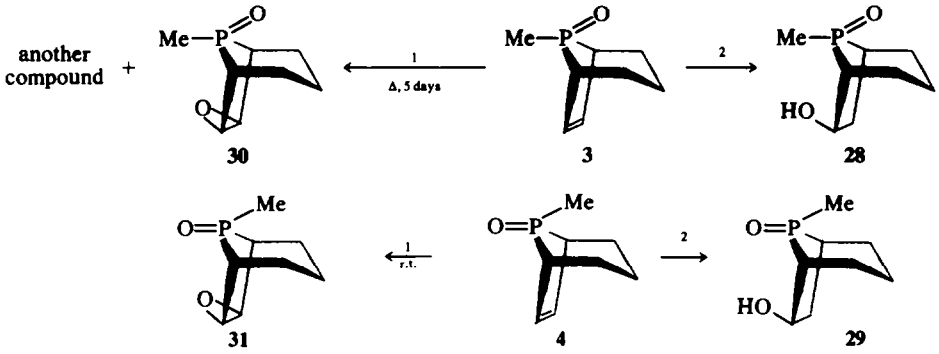
Table 3.



	H_6	$^3J_{PH_6}$* (φ_{PH_6})*	$J_{H_5H_6}$ ($\varphi_{H_5H_6}$)**	$J_{H_6H_{7(7')}}$ ($\varphi_{H_6H_7}$)**	H_7	$^3J_{PH_7}$ (φ_{PH_7})*	$J_{H_7H_1}$ ($\varphi_{H_1H_7}$)**
27 R=Ph 6β-Br 7α-Br	4·48dd	30 (150°)	0 (90°)	5·5 (110°)	4·43dd	0 (95°)	5·5 (30°)
20 R=Ph 6β-OH	4·23ddd	27·5 (150°)	0 (90°)	9·0; 4·0 (0°); (120°)	—	—	—
22 R=Ph 6α-OH	3·95m	0 (95°)	‡ (30°)	‡ (0°) (110°)	—	—	—
23 R=Ph 6β-OH 7β-OH	4·05d	29·0 (150°)	0 (90°)	—	4·05d	29 (150°)	0 (90°)
24 R=Ph 6,7β-epoxy	3·50dd	19·5 (180°) (120°)†	1 (65°) (0°)†	—	3·50dd	19·5 (180°) (130°)†	1 (65°) (0°)†
25 R=Ph 6α-Br 7β-OAc	4·16dd	0 95°	5·0 (30°)	5·0 (110°)	5·36dd	29 (150°)	0 (90°)
28 R=Me 6β-OH	4·26dm	28 (150°)	(0)‡ (90°)	(9·0) (4·0)‡ (0°) (110°)	—	—	—
30 R=Me 6,7β-epoxy	3·49dd	19·5 (180°) (120°)†	1 (65°) (0°)†	—	3·49dd	19·5 (180°) (130°)†	19·5 (65°) (0°)†
29 O=P-Me 6β-OH	4·20dm	28 (150°)	(0)‡ (90°)	(8·5) (4·5)‡ (0°) (110°)	—	—	—
31 O=P-Me 6,7β-epoxy	3·73dd	19 (180°) (120°)†	1 (65°) (0°)†	—	3·73dd	19 (180°) (130°)†	19 (65°) (0°)†

*The angles were measured from a Dreiding model. $^3J_{PH_{6(7)}}$—the dihedral angle between PC, $CH_{6(7)}$.
**The dihedral angle between the corresponding protons.
†The measured angles for the 6,7 α epoxy isomer.
‡The shape of the signal was not clear enough for J-measurements: in the case of **28** and **29**, J-values are given according to the corresponding acetates.

These observations were not too surprising in view of the great steric hindrance exerted on the C_6–C_7 double bond by the P-phenyl group from the β-direction and the C-3α-proton from the α-direction. Under very drastic conditions, namely boiling of **1** in EtOAc in the presence of large excess of *m*-chloroperbenzoic acid for 6–8 days, an epoxide (**24**) could at last be obtained but only in low yields. Furthermore this epoxide was accompanied by two other compounds, which resulted from the severe conditions; the structure of these compounds is the subject of a following report. The epoxidation turned out to be stereospecific giving only the β-epoxide, as could be judged from the $J_{H_5H_6}$ (or $J_{H_1H_7}$) and $^3J_{PH_{6(7)}}$ values (Table-3); indeed a change in the $^3J_{PH_{6(7)}}$ value, as compared to ogher compounds of this series was observed and this needs some explanation. In the case of phosphonates it has already been found that besides the influence of the PC,CH angle, the J-value is also affected by change of hybridization of the protons involved and changes in the P–C–C and C–C–H internal angles caused by strain of the molecule.[11] The J-values are decreased while these angles alter from the normal ones (~110°). Further evidence for the β-orientation of the epoxide (**24**) was obtained by its opening under acidic conditions. Unexpectedly, the oxiranic ring showed an outstanding stability towards different acidic conditions; 5–10%



SCHEME 4. 1. *m*-chloroperbenzoic acid; 2. B_2H_6.

$HClO_4$ in acetone or 4% HCl in iPrOH left this functional site unchanged. Only dissolving of **24** in 48% HBr in acetic acid brought about the opening of the epoxide ring to give the 6α - bromo - 7β - acetoxy derivative (**25**) (See Table-3) thereby confirming the epoxide configuration of **24**. The drastic conditions required for the oxirane ring opening may be explained, on ground of the steric hindrance of the C_6-C_7 bond, which was also responsible for the difficulties in the epoxidation, and prevents, to a great extent, the trans periplanar transition state required for the ring opening. This steric hindrance must be even stronger than the strain caused by the epoxide ring by itself. Existence of the strain could be seen apart from the $^3J_{PH}$ value, by the possibility to obtain the bromohydrine (**26**), by mild alkaline treatment of **25**, without closure to the epoxide as could be expected from a *trans*-bromohydrine.

The last reaction which was carried out on **1**, was its bromination under drastic conditions, after the addition at ambient temperature failed. A dibromide (**27**) could be obtained only after heating of **1** in acetic acid for 30 h in the presence of large excess of bromine. The compound obtained showed the expected NMR spectrum (Table-3) and by boiling with zinc in acetic acid gave back the starting olefin **1**, excluding any possible C-3α-H hydrid shift which could, a priori, be suspected according to the required conditions.

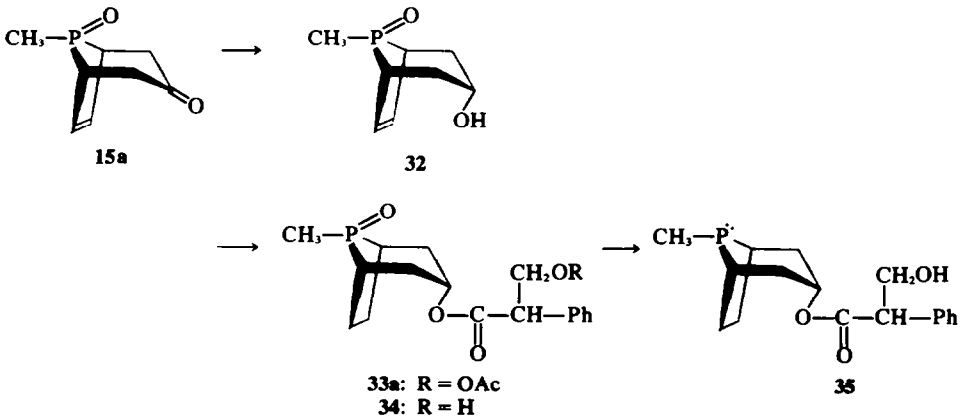
Hydroboration of **3** and **4** behave as **1** yielding the expected 6β-hydroxy derivative (**28** and **29** respectively) while epoxidation was different for the two (Scheme-4). Compound **3**, like **1**, demanded prolonged heating with the m-chloroperbenzoic acid, while **4** underwent the reaction even at r.t. to give **31** indicating clearly the less steric requirements of the P=O group as compared to the P–CH_3 group. In conclusion, the rate of steric hindrance caused, in the above mentioned ractions, by the various P-substituents, as compared to the C-3α-proton, can be summarized by the following sequence: C-3α-H > Ph–P > Me–P > O=P.

Once the stereochemistry as well as the chemical behaviour of the 8 - phosphabicyclic compounds was well established the following reactions were performed in order to convert compound **3** into the phosphaatropine analog.[14]

These phosphaatropines are now the subject of pharmacological investigation.

EXPERIMENTAL

M.ps were taken on a Unimelt Thomas & Hoover's Capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord model 337 spectrophotometer, UV spectra were recorded on a Perkin-Elmer 137UV spectrophotometer. NMR spectra were taken either on a Varian HA-100 spectrometer or a Jeol JNM-C-60HL spectrometer equipped with a heterodecoupler, 5–10% solution in $CDCl_3$ (unless otherwise



indicated), containing TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument.

Starting materials. 1,3-cycloheptadiene was prepared from cycloheptene according to the method described for the preparation of 1,3-cyclohexadiene,[15] (40%; b_{760} = 121°–123° (lit[16] 121°–122·5°)). 1 - Acetoxycyclohepta - 3,5 - diene was synthesized from 1,3,5 - cycloheptatriene (Fluka) in a method described elsewhere.[1] Phenyldibromophosphane was prepared from phenylphosphinic acid (Aldrich) and PBr_3 according to Quin's method.[4] Methyldibromophosphane was prepared from methyldichlorophosphane (Ethyl Co.) and PBr_3.[17] Phenyldichlorophosphane and ethyldichlorophosphane were commercially available (Aldrich and Ethyl Co., respectively).

8 - *Alkyl(Aryl)* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1.]*oct* - 6 - *enes—General procedure*

a. *Neat.* Equimolar quantities of the diene and RPX_2 were kept in sealed flasks (r.t.) or sealed tubes (elevated temp.), under N_2 in the presence of small amounts of a radical scavenger (hydroquinone or Cu-stearate). When no more change in the ppt could be observed, the tube, or flask, was opened and the crystalline or gummy ppt washed several times with petrol–ether to remove unreacted starting materials. The product was then reacted with equimolar amount of crushed ice, and the solution carefully neutralized with solid $NaHCO_3$. The water was removed under reduced pressure and the dry solid mixture was then extracted with hot $CHCl_3$ and EtOAc. The combined extracts were evaported to dryness, yielding the desired product(s).

b. *In petrol–ether solution.* The mixture of the two reactants was dissolved in dry petrol–ether (60°–80°; 1:2 V/V) under the same conditions as described for method *a*. When no further precipitation could be observed the solvent was decanted and the mixture worked-up in the same manner as described in procedure *a*.

8 - *Phenyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *ene* (**1**)

a. Cyclohepta - 1,3 - diene (24g) and $PhPBr_2$ (68·5 g) were kept under N_2 at r.t. for 6 days. After work-up the crude solid product was recrystallized from EtOH–EtOAc (27·8 g, 50%).

b. The mixture of the diene (32 g) and $PhPBr_2$ (92 g) was kept in petrol–ether (200 ml) for 7 months. The white ppt gave after the work-up compound **1** (24 g, 33%) m.p. 126°–127° (EtOH–EtOAc) ν_{max}^{KBr} 3020, 2955, 2900, 2840, 1610, 1590, 1450, 1350, 1260, 1190, 1160, 1110, 1070, 1040, 1010, 990, 960, 900, 800, 755, 715, 694, 645, 595, 500, 485 cm^{-1}. (Found: C, 71·49; H, 6·89; P, 13·85, $C_{13}H_{15}OP$ requires: C, 71·55; H, 6·93; P, 14·19%).

8 - *Ethyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *ene* (**2**)

Cyclohepta - 1,3 - diene (1·1 g) and $EtPCl_2$ (1·7 g) were heated in a sealed tube (100°) for 2 weeks. After cooling and work-up of the brown gummy product a very hygroscopic solid was obtained. Sublimation (90°/0·01 mm) gave pure **2** (0·7 g, 35%), m.p. 81°–83°. ν_{max}^{neat} 3025, 2925, 2850, 1460, 1350, 1290, 1270, 1190, 1155, 1050, 1030, 910, 810, 760, 720, 650 cm^{-1}. (Found: C, 63·75; H, 9·03; P, 18·22. $C_9H_{13}OP$ requires: C, 63·52; H, 8·88; P, 18·20%).

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *enes* (**3** *and* **4**)

a. Cyclohepta - 1,3 - diene (17·0 g) and methyldichlorophosphane (21·2 g) were heated in a sealed tube (N_2, Hydroquinone, 80°) for 4 days. The white solid product was worked up in the usual manner, resulting in an hygroscopic solid (25·0 g, 94%). The product consisted of two different components (according to T.L.C. and NMR spectrum). A sample of the crude product (1·5 g) was chromatographed on a neutral alumina column (Merck, grade III). Elution with methanol–EtOAc (1:9) yielded pure **3** (0·2 g), a mixture of **3** and **4** (~0·1 g), and pure **4** (1·0 g). (1·30 g, 87% overall yield). Compound **3** could be recrystallized under N_2 (cyclohexane) or sublimed (80°/0·15 mm). m.p. 97°–99°. ν_{max}^{KBr} 3030, 2900, 2840, 1460, 1320, 1290, 1190, 1150, 1050, 890, 780, 730, 650, 585 cm^{-1}. (Found: M^+ 156; $C_8H_{13}OP$ requires: MW 156). Compound **4** was purified by sublimation (100°/0·05 mm). m.p. 128°–129°, $\nu_{max}^{CHCl_3}$: 3030, 2920, 2850, 1620, 1470, 1460, 1430, 1350, 1310, 1290, 1190, 1150, 1100, 1045, 955, 940, 910, 870, 850, 650, 580 cm^{-1}. (Found: M^+ 156; $C_8H_{13}OP$ requires: MW 156).

b. Repetition on *a* [diene (0·94 g); $MePCl_2$ (1·17 g)] at room temp (3 months) yielded a mixture of **3** and **4** (0·9 g, 58% in a ratio of *ca* 1:2 respectively, according to NMR spectrum of the crude product).

c. Repetition on *b*, using $MePBr_2$ instead of $MePCl_2$ (5 days) gave a mixture of **3** and **4** (88%, in a ratio of *ca* 2:1 respectively.

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *en* - 3 - *yl* - *acetate* (**5** *and* **6**)

1 - acetoxycyclohepta - 3,5 - diene (16·0 g) and $MePCl_2$ (12·5 g) were kept in a sealed flask (N_2, hydroquinone) at room temp (2 months). The reddish viscous product was worked up in the usual procedure, yielding a very hygroscopic solid product (16·6 g).

A sample of the crude product (0·5 g) was chromatographed on a neutral Alumina column (Merck, grade III). Elution with EtOAc gave first a white hygroscopic solid (418 mg, **5** + **6** in a ratio of *ca* 95:5 according to NMR spectrum). Further elution (Me OH–EtOAc 1:5) gave a small amount of white solid (43 mg). This solid was identified (IR and NMR data) as a mixture of the corresponding alcohols of **5** and **6**.

The mixture (**5** + **6**) was recrystallized (EtOAc–ether) to give pure **5** (250 mg. 37%). m.p. 148°–149°. ν_{max}^{KBr}: 3030, 2950, 2900, 2850, 1740, 1620, 1390, 1310, 1240, 1240, 1215, 1190, 1130, 885, 745, 715, 650, 570 cm^{-1}. (Found: C, 56·59; H, 7·25; P, 15·01. $C_{10}H_{15}O_3P$ requires: C, 56·07; H, 7·06; P, 14·46%).

8 - *Phenyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *en* - 3 - *yl* - *acetate* (**7**)

Compound **7** was obtained in low yields from the diene and $PhPCl_2$ under several different conditions, as described in a previous report.[1]

8 - *Methyl* - 8 - *phenyl* - 8 - *phosphoniumbicyclo*[3.2.1]*oct* - 6 - *en* *iodide* (**9**)

A sample of the adduct obtained from 1,3-cycloheptadiene and $PhPBr_2$ (5·5 g) was suspended in dry THF (30 ml) under N_2, and Mg turnings (0·45 g) were added to the stirred suspension. A vigorous exotermic reaction started immediately, and calmed down after several minutes. The reaction mixture was refluxed (6 h), then the solvent was distilled out under N_2, and the residue oil dissolved in acetone (20 ml). Excess of MeI was added to the stirred solution, causing a rapid precipitating of a white solid. The product was collected and recrystallized (EtOH–EtOAc). (1·5 g, 29%). m.p. 233°. ν_{max}^{KBr}: 3000, 2920, 2850, 1620, 1435, 1330, 1290, 1260, 1205, 1175, 1150, 1110, 1045, 955, 910, 880, 810, 790, 745, 720, 685, 585, 490 cm^{-1}. δ 1·50–2·50 m (H_2, H_3, H_4, 6H); 2·65 d (^2JPH = 15 Hz; P–CH_3, (3H); 4·05 dm ($^2JPH_1(H_5)$ = 12 Hz; $H_1(H_5)$, 2H); 6·20 dm ($^3JPH_6(H_7)$ = 21 Hz; $H_6(H_7)$, 2H); 7·55 m, 8·08 dm (^2JPH = 12 Hz). (Ph–H, 5H) ppm. (Found: C, 48·79; H, 5·26; P, 8·90; $C_{14}H_{18}PI$ requires: C, 48·79; H, 5·27; P, 8·99%).

8 - *Phenyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*octane* (**11**)

Compound **1** (1·0 g) in EtOH (15 ml) was hydrogenated in a Parr (60 psi) over RaNi at room temp (48 h). After filtration of the catalyst and evaporation of the solvent, an hygroscopic white solid was obtained (0·97 g, 97%). The product could be purified by recrystallization under N_2 (benzene–hexane). m.p. 121°–123°. ν_{max}^{KBr} 3000, 2930, 2830, 1590, 1470, 1450, 1350, 1310, 1180, 1125, 1110, 1050, 1035, 990, 960, 915, 875, 860, 785, 760, 740, 700, 615, 515,

505 cm^{-1}. δ 1·20–2·80 brm (All the skeleton protons, 12H); 7·30–7·90 m (Ph–H, 5H) ppm. (Found: C, 70·84; H, 7·72; P, 13·98. $C_{13}H_{17}OP$ requires: C, 70·87; H, 7·78; P, 14·06%).

Thioketalization of 8 - *phenyl* - 8 - *oxo* - 8 - *phosphabicyclo* [3.2.1]*octan* - 3 - *one* **8a** (**10**)

To a soln of **8a** (234 mg) in AcOH (5 ml), ethane - 1,2 - dithiole (0·3 ml) and $BF_3:Et_2O$ (0·3 ml) were added. The mixture was kept in r.t. for 72 h, during which white solid precipitated. The product was collected and washed with several portions of ether. (245 mg, 80%). m.p. 208–209°, ν_{max}^{KBr}: 3050, 2900, 2825, 1590, 1460, 1445, 1350, 1310, 1275, 1250, 1230, 1170, 1150–1080, 1020, 940–910, 895, 750, 740, 690, 630, 560–530 cm^{-1}, δ 1·58–1·76 m (H_{6_n}, H_7; 2H); 2·10 m (H_{2eq}, H_{4eq}; 2H); 2·40–2·68 m (H_6, H_7, H_1, H_5; 4H); 2·76–3·04 m (H_{2ax}, H_{4ax}; 2H); 3·34 m ($(SCH_2)_2$; 4H); 7·46–7·90 m (Ph; 5H).

Desulfurization of **10** (**11**)

A soln of **10** (25 mg) in EtOH (25 ml) was refluxed (6 h) in the presence of RaNi (15 mg). The catalyst was filtered, after cooling, and the solvent stripped of under reduced pressure, yielding hygroscopic white solid (16 mg, 89%). The product was identical to **11** according to its m.p. (122°–123°), IR and NMR spectra.

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *en* - 3β - *ol* (**14**)

Compound **5** (2·1 g) was dissolved in 1% KOH/MeOH soln (1 ml) and kept at room temp (2 h), then neutralized (1% HCl/isopropanol) and the solvents were removed under reduced pressure. The obtained solid was extracted with hot $CHCl_3$ (25 ml). Removing the solvent gave white solid which was recrystallized from either EtOH–EtAOc or CH_3CN, yielding pure **14a** (1·4 g, 85%). m.p. 224°–225°, ν_{max}^{KBr}: 3280, 2900, 2830, 1430, 1370, 1300, 1260, 1190–1150, 1050–1030, 880, 750, 650, 590 cm^{-1}, δ 1·50 d (^2JPH = 13 Hz; P–CH_3, 3H); 2·05–2·20 m ($H_2(H_4)$, 4H); 2·55 dm ($^2JPH_1(H_5)$ = 11 Hz; $H_1(H_5)$, 5H); 3·55 m (quintet-like) (H_{3ax}, 1H); 6·10 dm ($^3JPH_6(H_7)$ = 18 Hz; $H_6(H_7)$, 2H) ppm. (Found: M^+ 172; $C_8H_{13}O_2P$ requires: MW 172).

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 6 - *en* - 3 - *one* (**15a**)

A soln of **14a** (1·0 g) in acetone–$CHCl_3$, (1:1; 80 ml) was treated with Jones reagent (5 ml) at room temp. After 2 h of stirring, the soln was concentrated to about $\frac{1}{10}$ of its volume, water (10 ml) was added and the soln neutralized (solid $NaHCO_3$). The solvents were then evaporated to dryness and the solid residue extracted with hot $CHCl_3$ (50 ml) and EtOAc (50 ml). Removing of the solvents from the combined extracts gave a white solid product (1·03 g). Recrystallization (EtOAc–cyclohexane) gave pure **15a**, (880 mg, 89%), m.p. 178°–179°, ν_{max}^{KBr}: 2930–2850, 1705, 1440, 1380, 1330, 1290, 1180, 1145, 995, 960, 760, 625 cm^{-1}, δ 1·65 d (^2JPH = 13 Hz; P–CH_3, 3H); 2·91 m ($\nu A = 2{\cdot}64$; $\nu B = 3{\cdot}18$; JAB = 15 Hz; $^3JPH_2(H_4)^{ax}$ = 6 Hz; $^3JPH_2(H_4)^{eq}$ = 27 Hz; $JH_1H_2 = JH_4H_5$ = 4 Hz; $H_2(H_4)$, 4H); 2·75 dm ($^2JPH_1(H_5)$ = 13·5 Hz; $H_1(H_5)$, 2H); 6·38 dm ($^3JPH_6(H_7)$ = 18 Hz; $H_6(H_7)$, 2H) ppm. (Found: M^+ 170; $C_8H_{11}O_2P$ requires: MW 170).

Thioketalization of **15a** *to* **16**

The thioketal **16** was prepared from ketone **15a** (0·1 g) under the conditions described for thioketal **10**. m.p. 204°–206°, ν_{max}^{KBr}: 3020, 2870, 1440, 1370, 1325, 1300, 1270, 1235, 1180, 1155, 1110, 900, 890, 850, 830, 770, 730, 650, 605, 515 cm^{-1}, δ 1·52 d (^2JPH = 13 Hz; P–CH_3, 3H); 3·13 s (Thioketalic protons 4H); 6·28 dm ($^3JPH_6(H_7)$ = 18 Hz; $H_6(H_7)$, 2H); 2·20 – 3·20 m (all other protons, 6H) ppm. (Found: M^+ 246; $C_{10}H_{15}OPS_2$ requires: MW 246).

Desulfurization of **16** *to* **17**

Compound **17** was obtained from **16** by the method used for preparation of **11**. The white, hygroscopic solid obtained (29 mg) was identical according to its spectral data to the compound prepared by the catalytic hydrogenation of **3**.

Hydrogenation of **3** *to* **17**

Compound **3** (100 mg) in EtOH (15 ml) was hydrogeneated over RaNi under atmo pressure at r.t. (15 h), yielding white, highly hygroscopic solid (100 mg), which could be recrystallized (cyclohexane) under N_2, m.p. 135° (Sub. 90°/0·1), ν_{max}^{KBr}: 2910–2820, 1320, 1300, 1190, 1155, 1030, 950, 910, 895, 770, 600 cm^{-1}, δ 1·46 d (^2JPH = 13 Hz; P–CH_3, 3H); 1·40–2·60 m (All the skeleton protons, 12H) ppm. (Found: M^+ 158; $C_8H_{15}OP$ requires: MW 158).

Hydrogenation of **4** *to* **18**

Hydrogenation of **4** (120 mg) was carried out as for **3**, yielding white, highly hygroscopic solid (115 mg). m.p. 150° (Sub. 100°/0·07) $\nu_{max}^{Nast.}$: 2920–2850, 1490, 1400, 1340, 1290, 1220, 1140, 1100, 955, 900, 885, 780, 710, 620 cm^{-1}, δ 1·70 d (^2JPH = 13 Hz; P–CH_3, 3H); 1·30–2·40 m (All the skeleton protons, 12H) ppm. (Found: M^+ 158; $C_8H_{15}OP$ requires: MW 158).

Reduction of **21** *to* **20** *and* **22**

a. *Catalytic hydrogenation.* Hydrogenation of **21** (0·1 g) over RaNi yielded white solid (80 mg), which was identical to the alcohol **20** according to its m.p. and spectral data.

b. $NaBH_4$. The ketone **21** (70 mg) in MeOH (5 ml) was treated with $NaBH_4$ (30 mg). After the usual work-up, a white solid (70 mg) was obtained, consisting of **20** and **22** (2:1), according to the NMR spectrum.

Hydroboration of **1** *to* **20**

A suspension of $NaBH_4$ (3·5 g) in dry diglyme (50 ml) was dropwise added into a stirred soln of **1** (3·0 g) together with BF_3–etherate (15 g) in dry diglyme (70 ml). The mixture was then stirred at r.t. (1 h) and for an additional h at 70°–80°. After cooling, water (10 ml) was added, followed by a soln of 3N NaOH (70 ml). A soln of 30% H_2O_2 (25 ml) was dropwise added to the mixture, which was then diluted with cold water (15 ml) and extracted with $CHCl_3$ (5 × 50 ml). The combined extracts were washed with water, dried (Na_2SO_4) and the solvent evaporated to dryness. The solid product was recrystallized from EtOH–EtOAc (2·90 g, 89%). m.p. 230°–231°, ν_{max}^{KBr}: 3250, 3030, 2930–2830, 1590, 1440, 1320, 1290, 1160, 1100, 1040, 1025, 965, 905, 845, 785, 745, 730, 680, 605, 580, 485 cm^{-1}, δ ($CDCl_3$) 4·25 dm ($^3JPH_6$ = 29 Hz; H_{6a}, 1H); 7·40–7·95 m (Ph–H, 5H); 1·20–2·80 m (All other protons, 10H) ppm. (Found: C, 66·02; H, 7·23; P, 13·30; $C_{13}H_{17}O_2P$ requires: C, 66·09; H, 7·25; P, 13·54%).

Oxidation of **20** *to* **21**

Alcohol **20** (0·5 g) was oxidized by Jones reagent under conditions used for oxidation of **15a**. The product (485 mg 98%) obtained, was recrystallized from EtOAc, m.p. 119°–120°, ν_{max}^{KBr}: 3025, 2990, 2930, 2845, 1725, 1440, 1410, 1390, 1200, 1170, 1150, 1110, 1030, 1000, 900, 810, 790, 745, 730, 695, 615, 590, 540, 490 cm^{-1}, δ 1·60–3·20 m(broad) (All the skeleton protons, 10H); 7·35–7·70 m (Ph–H, 5H) ppm. (Found: M^+ 234; $C_{13}H_{15}O_2P$ requires: MW 234).

Oxidation of **1** *with* OsO_4 *to* **23**

Compound **1** (0·85 g) in pyridine (15 ml) were stirred together with OsO_4 (1·0 g) for 2 h. The mixture was diluted with $NaHSO_3$ (1·8 g in 30 ml of water) and pyridine (20 ml). The resulted soln was continuously extracted with $CHCl_3$. The chloroformic soln was washed with HCl, water, then dried (Na_2SO_4) and the solvent removed under reduced pressure, yielding a viscous oil (670 mg). The crude product was chromatographed on a neutral alumina

column (Merck grade III). Elution with EtOAc gave unreacted **1** (350 mg) and pure **23** (290 mg, 29%). Compound **23**, (highly hygroscopic white solid) was recrystallized from EtOH–EtOAc, m.p. 240°C (not sharp), ν_{max}^{KBr}: 3400, 3100, 2960, 2930, 2870, 1590, 1490, 1460, 1440, 1400, 1330, 1280, 1260, 1185, 1155, 1115, 1090, 1065, 1045, 995, 970, 950, 910, 855, 815, 745, 695, 605, 570, 530, 500 cm^{-1}, δ 4·08 d ($^3JPH_6(H_7)$ = 30 Hz; $H_6(H_7, 2H)$; 7·20 – 7·85 m (Ph–H, 5H); 1·20–2·50 (All other protons, 10H) ppm. (Found: M^+ 252; $C_{13}H_{17}O_3P$ requires: MW 252).

Epoxidation of **1** *to* **24**

Compound **1** (8·6 g) and *m*-chloroperbenzoic acid (80%, 20 g) were heated in EtOH (90°, 98 h). Peracid (5 g) was added after each period of 24 h. After cooling, the *m*-chlorobenzoic acid was filtered, and the soln was diluted with chloroform (500 ml), washed with 10% $NaHCO_3$ aq. to remove any residual acid, then water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residual oily product (4·5 g) was chromatographed on a neutral alumina column (Merck, grade III). Elution with benzene–EtOAc (4:1) gave an oily by-product (1·3 g) proved to be Ethyl-*m*-chlorobenzoate by its NMR spectrum. After this compound, an unknown product was eluated (492 mg), then a mixture of this product, residual unreacted **1** and a second unknown compound (1·056 g). The pure second unknown product was then eluted (740 mg) followed by a mixture with the epoxide **24** (140 mg) and at last the pure epoxide **24** (1·013 g).

The epoxide (hygroscopic white solid) was recrystallized from cyclohexane. m.p. 127°–130°, ν_{max}^{KBr}: 3040, 3000, 2930, 2850, 1590, 1450, 1280, 1240, 1210, 1180, 1160, 1115, 960, 890, 830, 750, 700, 630, 570 cm^{-1}, δ 3·50 dm ($^3JPH_6(H_7)$ = 22·6 Hz; $H_6(H_7)$, 2H); 7·43 m (3H), 7·70 m (2H) (Ph–H); 1·60–2·90 m (all other protons, 10H) ppm. (Found: C, 66·46; H, 6·45; P, 13·14; $C_{13}H_{15}O_2P$ requires: C, 66·66; H, 6·45; P, 13·22%).

Acidic ring opening of **24** *to* **25** *and* **26**

Compound **24**, (422 mg) dissolved in a soln of 48% HBr/HOAc (5 ml), was kept at r.t. (3 days). The mixture was diluted with H_2O (10 ml), neutralized (solid $NaHCO_3$) and extracted with $CHCl_3$ (5 × 25 ml). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness, yielding a brown viscous oil (643 mg). A yellow crystalline product (135 mg) separated on attempt to crystallize the crude product. It was found that the crystalline product is the corresponding bromohydrine **26**. Recrystallization from EtOH (103 mg). m.p. 252–253°, ν_{max}^{KBr}: 3230, 3030, 2930, 2850, 1590, 1445, 1340, 1310, 1180, 1150, 1110, 1035, 965, 930, 910, 855, 810, 790, 750, 740, 690, 590, 550, 500, 480, 450 cm^{-1}, δ (d_6-DMSO) 3·95 t ($J_{H_6H_7} = J_{H_5H_6}$ = 5 Hz; H_6); 4·48 dd ($^3J_{PH_7}$ = 29 Hz; $J_{H_6H_7}$ = 5 Hz; H_7); 7·35–8·05 m (Ph, 5H); 1·40–3·15 m (all other protons; 8H). (Found: M^+ 315; $C_{13}H_{16}O_2PBr$ requires: MW 315). The residual brownish viscous oil (mainly compound **25**) was chromatographed on a neutral alumina column (Merck, grade III; benzene–EtOAc; 3:1), leading to compound **25**, ν_{max}^{Neat}: 3050, 2950, 2880, 2860, 1745, 1595, 1470, 1440, 1375, 1310, 1295, 1230, 1200, 1160, 1100, 1080, 1050, 1000, 970, 900, 865, 850, 810, 795, 750, 730, 690, 640, 620, 610 cm^{-1}, δ (1·80 s ($OCCH_3$, 3H); 4·16 t ($JH_7H_6 = JH_5H_6$ = 5 Hz; H_6, 1H); 5·36 dd ($^3JPH_7$ = 29 Hz; JH_6H_7 = 5 Hz; H_7, 1H); 1·40–2·90 (all other skeleton protons, 10H); 7·30–8·00 m (Ph–H, 5H) ppm. (Found: M^+ 357; $C_{15}O_{18}O_3PBr$ requires: MW 357).

Bromination of **1** *to give dibromide* **27**

Bromine (0·8 ml) was added to a soln of **1** (2·2 g) in AcOH (50 ml). The mixture was heated (90°–100°) for 15 h, then another portion of Br_2 (0·8 ml) was added and the heating continued for additional 15 h. The soln was diluted with $CHCl_3$ (150 ml) and water (25 ml). The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3 × 30 ml). The combined chloroformic solns were washed with a 5% $Na_2S_2O_3$ aq (25 ml), then 10% $NaHCO_3$ aq (15 ml) and water. After drying (Na_2SO_4) and evaporation of the solvent a solid product (2·56 g, 67%) was obtained. Recrystallization from EtOH–EtOAc. m.p. 167°–169°, ν_{max}^{KBr}: 3040, 2980, 2930, 2900, 2850, 1590, 1440, 1295, 1190, 1165, 1115, 1040, 970, 910, 850, 810, 790, 750, 730, 690, 640, 535, 490 cm^{-1}, δ 4·46 dd ($JH_1H_{7\beta} = JH_{6\alpha}H_{7\beta}$ = 6 Hz; $H_{7\beta}$, 1H); 4·58 dd ($^3JPH_{6\alpha}$ = 28 Hz; $JH_{7\beta}H_{6\alpha}$ = 6 Hz; $H_{6\alpha}$, 1H); 7·44–7·90 m (Ph–H), (5H); 1·64–3·04 m (broad) (All other protons, 8H) ppm. (Found: C, 41·38; H, 4·10; P, 8·18; Br, 42·51; $C_{13}H_{15}OPBr_2$ requires: C, 41·30; H, 3·99; P, 8·19; Br, 42·28%).

Debromination of **27**

A soln of **27** (0·2 g) in $CHCl_3$ (20 ml) and HOAc (3·0 ml) was refluxed (15 h) in the presence of Zn powder (0·2 g). After cooling, the soln was diluted with $CHCl_3$ (50 ml), the solid residue filtered out and the soln washed with water, (10 ml), 10% $NaHCO_3$ aq (15 ml) and again with water. After drying (Na_2SO_4) and evaporation of the solvent, a white solid was obtained (120 mg). The recrystallized product (EtOAc) was identical to **1** according to its m.p., IR and NMR spectra.

Hydroboration of **3** (**28**)

Hydroboration of **3** (200 mg) under the conditions described for preparing **20** gave **28** (157 mg) as a hygroscopic white solid, m.p. 57°–60° (for the acetate), ν_{max}^{Neat}: 3550–3350, 2950, 2900, 2830, 1450, 1420, 1320, 1270, 1190, 1150, 1120, 1045, 1030, 975, 950, 900, 885, 850, 810, 780, 745, 710, 670 cm^{-1}, δ 1·72 d (^2JPH = 13 Hz; P–CH_3, 3H); 4·25 dm ($^3JPH_6$ = 28 Hz; H_6, 1H); 1·30–2·30 m (all other protons, 10H) ppm. (Found: M^+ 174; $C_8H_{15}O_2P$ requires: MW 174).

Hydroboration of **4** (**29**)

Hydroboration of **4** under the conditions described for **3** (570 mg) yielded highly hygroscopic white solid (560 mg). m.p. 154°–156° (for the acetate) ν_{max}^{Neat}: 3390 br, 2930–2860, 1450, 1410, 1345, 1300, 1235, 1215, 1170, 1120, 1090, 1050, 1030, 980, 950, 870, 780, 740, 705 cm^{-1}, δ 1·71 d (^2JPH = 13 Hz; P–CH_3, 3H); 4·20 dm ($^3JPH_6$ = 28·5 Hz, H_6, 1H); 1·26–2·40 m (all other protons, 10H) ppm. (Found: M^+ 174; $C_8H_{15}O_2P$ requires: MW 174).

Epoxidation of **3** (**30**)

Compound **3** (1·1 g) in EtOAc (20 ml) was treated with a great excess of *m*-chloroperbenzoic acid (80%, a total amount of 6·65 g) under conditions described for the epoxidation of **1**. Chromatography of the crude product (1·54 g) yielded ethyl-*m*-chlorobenzoate (440 mg), then an unknown product (415 mg) followed by the epoxide **30** (341 mg), as a clear, viscous oil (MeOH–EtOAc 1:50), ν_{max}^{Neat}: 2980, 2915, 2850, 1460, 1445, 1400, 1300, 1245, 1210, 1185, 1150, 960, 940, 885, 840, 780, 710, 620 cm^{-1}, δ 1·70 d (^2JPH = 13·5 Hz; P–CH_3, 3H); 3·52 dm ($^3JPH_6(H_7)$ = 22·5 Hz; $H_6(H_7)$, 2H); 1·50–2·60 m (all other protons, 10H) ppm. (Found: M^+ 172; $C_8H_{13}O_2P$ requires: MW 172).

Epoxidation of **4** (**31**)

A mixture of **3** and **4** (9·5 g) in CH_2Cl_2 (75 ml) was treated with *m*-chloroperbezoic acid (5·0 g) at r.t. (15 h). The white ppt (*m*-chlorobenzoic acid) was filtered, the soln was diluted with CH_2Cl_2 (500 ml). Residual acid was removed by washing the organic soln with portions of 10% $NaHCO_3$ aq. The soln was washed with water, dried and evaporated to dryness, yielding a solid product (6·0 g), which, according to NMR spectrum, proved to be almost pure compound **3**.

The aqueous layer was evaporated to dryness under reduced pressure. The residue was extracted with hot EtOAc (100 ml). The extract yielded after removing the solvent, white amorphous and highly hygroscopic solid. (2·77 g), ν_{max}^{Neat}: 2980, 2930, 2900, 2850,

1450, 1410, 1395, 1370, 1280, 1265, 1230, 1180, 1130, 1090, 1060, 1045, 955, 940, 880, 830, 805, 770, 730, 780, 675, 620 cm^{-1}, δ 1·70 d (^2JPH = 13·5 Hz; P–CH_3, 3H); 2·70 dm ($^2JPH_1(H_5)$ = 12 Hz, $H_1(H_5)$, 2H); 3·75 dm ($^3JPH_6(H_7)$ = 18 Hz; $H_6(H_7)$, 2H); 1·40–2·90 m (all other protons, 6H) ppm. (Found: M^+ 172; $C_8H_{13}O_2P$ requires: MW 172).

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo* [[3.2.1]*octan* - 3 - *ol* (**32**)

The ketone **15a** (525 mg) in EtOH (35 ml) was hydrogenated over RaNi under atm pressure (18 h). After filtration of the catalyst, the solvent was evaporated to yield a white solid (470 mg, 87%). The product was recrystallized from CH_3CN m.p. 197°–198°, ν_{max}^{KBr}: 3250, 2910–2850, 1490, 1370, 1325, 1150, 1120, 1065, 1050, 950, 910, 870, 770, 680, 600, 490, 450 cm^{-1}, δ 1·50 d (^2JPH = 13 Hz; P–CH_3, 3H); 4·15 m (triplet-like) ($H_{3\beta}$, 1H); 1·40–3·10 m (all other protons, 10H) ppm. (Found: M^+ 174; $C_8H_{15}O_2P$ requires: MW 174).

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 3 - *yl* - *acetyltropate* (**33**)

A mixture of **32** (300 mg) and acetyltropoyl chloride (390 mg) was heated (75°) for 4 h. The viscous oily product was chromatographed on a neutral silica column (Merck, 7734). Elution with MeOH–EtOAc (1:5) gave pure **33** as a clear, viscous oil (380 mg, 61%). ν_{max}^{Neat}: 3030, 3000, 2940, 1745, 1600, 1510, 1470, 1390, 1340, 1230, 1200, 1160, 1120, 1020, 950, 910, 875, 760, 700, 680 cm^{-1}, δ 1·48 d (^2JPH = 13 Hz; P–CH_3, 3H); 2·03 s ($OCOCH_3$, 3H); 3·75–4·83 m (–CH–CH_2O–; 3H); 5·18 m (triplet-like ($H_{3\beta}$, 1H); 7·30 s (Ph, 5H); 1·30–3·00 m (All other protons, 10H) ppm. (Found: M^+ 364; $C_{19}H_{25}O_5P$ requires: MW 364).

8 - *Methyl* - 8 - *oxo* - 8 - *phosphabicyclo*[3.2.1]*oct* - 3 - *yl* - *tropate* (**34**)

To a soln of the ester **33** (380 mg) in dioxane (10 ml), a soln of 1·5% HCl aq (1 ml) was added. The reaction mixture was kept at 75° (18 h). After cooling, the soln was diluted with $CHCl_3$ (50 ml), neutralized K_2CO_3) and dried (Na_2SO_4). Filtration of the solids and evaporation of the solvent under reduced pressure, yielded clear, white, viscous oil. The product was purified by a chromatography on a small silica column. (291 mg, 82%), ν_{max}^{Neat}: 3350, 2920, 2850, 1740, 1600, 1540, 1505, 1470, 1370, 1280, 1150, 1110, 1020, 950, 910, 870, 770, 730, 700 cm^{-1}, δ 1·48 d (^2JPH = 13 Hz; P–CH_3, 3H); 3·40–4·40 m (–CH–CH_2OH, 3H); 520 m (triplet-like; $H_{3\beta}$, 1H); 7·30 m (Ph–H, 5H); 1·20–3·00 m (All other protons, 10H) ppm. (Found: M^+ 322; $C_{17}H_{22}O_4P$ requires: MW 322).

8 - *Methyl* - 8 - *phosphabicyclo*[3.2.1]*oct* - 3 - *yl* - *tropate* (**35**)

A soln of compound **34** (250 mg) in sodium-dried benzene (10 ml), to which trichlorosilane (1/2 g) was added in one portion under N_2 atm, was heated for 1 h at 50°. After the usual work-up a colorless viscous oil (150 mg) was obtained.

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