**Method G.** (a) A solution of Na (1.6 g, 0.06 g-atom) in EtOH (55 ml) was treated with 2-nitrophenol (8.8 g, 0.063 mol) and 1-chloro-2-butene (5 g, 0.055 mol) gradually added with stirring. The stirred solution was refluxed for 4.5 h, then further 1-chloro-2-butene (1 g, 0.0112 mol) and some KI were added, and refluxing was continued overnight. The EtOH was evaporated off under reduced pressure; the residue was treated with $H_2O$ and extracted with $Et_2O$. The ethereal solution was washed with 2 N NaOH solution and with $H_2O$, dried ($Na_2SO_4$), filtered, and evaporated to give 1-(2-butenyloxy)-2-nitrobenzene (8 g, 67%), bp 111 °C (0.08 mm). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

(b) 1-(2-Butenyloxy)-2-nitrobenzene (3 g, 9.6 mmol) was heated at 170–200 °C for 5 h. The cooled reaction mixture was dissolved in $Et_2O$ and extracted with 2 N NaOH. The alkaline solution was stirred with C, filtered through Supercel, acidified with HCl, and extracted with $Et_2O$. The ethereal solution was dried, treated with C, filtered, and evaporated to give 2-(1-buten-3-yl)-6-nitrophenol (1.85 g, 62%), bp 88 °C (0.35 mm). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

**Method H.** 2-(1-Buten-3-yl)-6-nitrophenol (27.17 g, 0.14 mol) in 90% MeOH (344 ml) with $NH_4Cl$ (20.64 g, 0.39 mol) was stirred at 60 °C and Zn powder (86 g, 1.3 g-atom) added over 40 min. The mixture was stirred and refluxed for 2.5 h and filtered through Supercel. The solution was evaporated, treated with $H_2O$, and extracted with $CHCl_3$ and the $CHCl_3$ was extracted with 2 N HCl. The HCl was neutralized with $NaHCO_3$ and the product extracted with $CHCl_3$, dried ($Na_2SO_4$), filtered, and evaporated to give 2-hydroxy-3-(1-buten-3-yl) aniline (14.17 g, 62%) as golden plates, mp 47–48.5 °C, from petroleum ether (bp 40–60 °C). Anal. ($C_{10}H_{13}NO$) C, H, N.

**Method I.** 2-Hydroxy-3-(1-buten-3-yl)aniline (14.17 g, 0.087 mol) in pyridine (45 ml) with benzoyl chloride (11.4 ml, 0.096 mol) when subjected to conditions of method A gave a 65% pure sample of 2-phenyl-7-(1-buten-3-yl)benzoxazole (15.82 g): NMR ($CCl_4$) $\delta$ 1.53 (3 H, d), 3.98 (H, m), 4.9–5.3 (2 H, m), 5.78–6.5 (H, m), 6.95–7.8 (6 H, m), 8.12–8.50 (2 H, m).

Similarly were prepared 2-(4-methylphenyl)- and 2-(4-chlorophenyl)-7-(1-buten-3-yl)benzoxazoles.

**Method J.** The 65% pure 2-phenyl-7-(1-buten-3-yl)benzoxazole (15.8 g) in $Me_2CO$ (350 ml) with $KIO_4$ (105 g, 0.46 mol) was stirred and treated with $KMnO_4$ (10 g, 0.063 mol) in $H_2O$ (500 ml) at 5–10 °C under $N_2$ while $Me_2CO$ (500 ml) was added simultaneously. The mixture was stirred overnight and then filtered. The filtrate was evaporated and the residue treated with $H_2O$ and extracted with $CHCl_3$. The $CHCl_3$ was extracted with 2 N NaOH and, after acidification of the aqueous phase, the product was extracted with $CHCl_3$, which was dried ($Na_2SO_4$), filtered, and evaporated to yield 2-phenyl-$\alpha$-methyl-7-benzoxazoleacetic acid, which was then purified as in Table I.

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# Butyrophenones from the Isomeric 2-Amino-5-phenylbicyclo[3.3.1]nonanes

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The preparation of 5-phenylbicyclo[3.3.1]nonan-2-one is described starting from the ketal of 4-phenyl-4-(2-carbethoxyethyl)cyclohexan-1-one. The ketone was then taken on to the butyrophenone derivatives of *endo*- and *exo*-5-phenylbicyclo[3.3.1]nonyl-2-amine. CNS screening results of these compounds are described.

Piperidines bearing a *p*-fluorobutyrophenone moiety on nitrogen and an aromatic ring in the vicinity of the 4 position have proven an unusually rich source for neuroleptic agents.[1] It is of interest that wide structural latitude maintains as to the nature of the attachment of the aryl group. We have shown that environment about nitrogen can be similarly modified; butyrophenones of 4-phenylcyclohexylamine exhibit good psychotropic activity.[2] Both piperidines and cyclohexylamines possess conformational freedom; it was of some interest to ascertain the biological activity of analogues containing nitrogen attached to a rigid cyclohexyl fragment.

**Chemistry.** Internal alkylation provided access to the requisite intermediate 5-phenylbicyclo[3.3.1]nonan-2-one (4). Thus, reduction of ester ketal 1[3] gave the corresponding alcohol 2; this was then converted to the mesylate and hydrolyzed to give the ketone 3. Treatment of that intermediate with *t*-BuOK in THF afforded the desired bicyclic ketone 4 in 78% yield.

Reduction of the ketone by means of $NaBH_4$ gave a single alcohol, in contrast to the observation on the corresponding 4-arylcyclohexanones.[2] This is assigned the configuration 5 based on the known propensity of this reaction to give equatorial alcohols. The NMR spectrum of the mesylate 6 (carbinyl H, seven-line pattern centered at $\delta$ 5.0) supports this assignment. The mesylate was then taken on to the axial butyrophenone (9) by standard manipulations.

Preparation of the epimer started by conversion of the ketone to the oxime 10; reduction of the corresponding acetate 11 by means of diborane gave a primary amine 12 clearly different from 8. This was then taken on to the butyropheone 13.

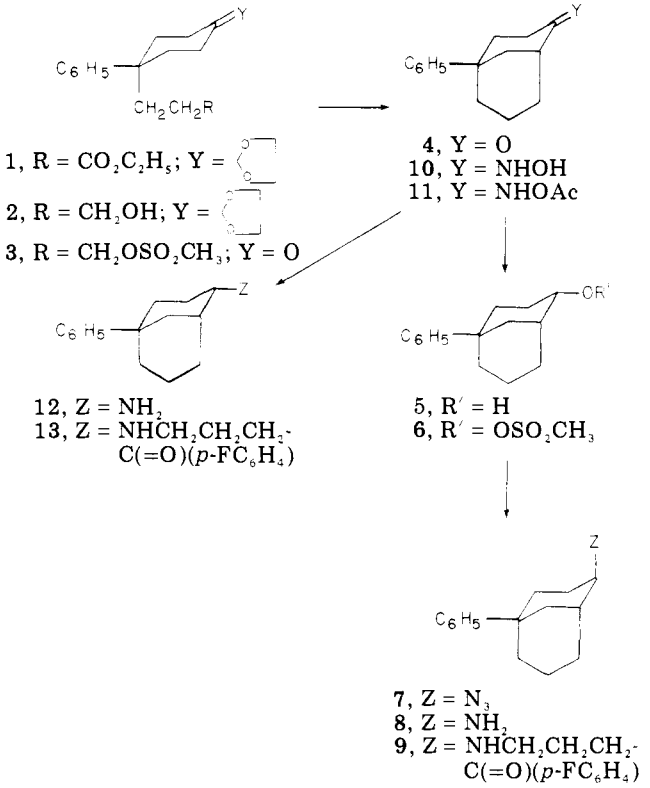
**Pharmacology.** The effects of the compounds on overt behavior as well as nicotine toxicity in mice were determined using procedures described earlier.[4] The results are listed in Table I.

The present compounds show a great diminution in activity from the corresponding cyclohexylamines[2] using nicotine antagonism as an index of potency. The relative configuration of the amine and nitrogen seems to have little effect on the biological activity of these compounds.

Table I. Pharmacological Testing Results[a]

| | $TR_{50}$[b] | $CH_{50}$[b] | $D_{50}$[b] | $P_{50}$[b] | Nicotine TE[b] | Nicotine L[b] |
|---|---|---|---|---|---|---|
| 9 | 13 | 9 | 6.3 | 18 | 20 | 18 |
| 13 | 71 | 18 | 18 | 32 | 16 | 16 |
| Haloperidol | 2.0 | 4 | 1.4 | 2.3 | 9 | 10 |

[a] Carworth Farm male albino mice (CF-1, 18–22 g) were administered the compounds ip as solutions or suspensions in 0.25% aqueous methylcellulose solution. [b] $TR_{50}$, traction; $CH_{50}$, chimney; $D_{50}$, dish; $P_{50}$, pedestal; antagonism of nicotine induced tonic extensor convulsion (TE) and death (L).




These particular analogues have been rendered rigid by the addition of three methylene groups to the active compounds. Whether the loss in activity is due to rigidity or increased lipophilicity (or even steric interaction) thus remains an unanswered question.

## Experimental Section

Melting points are uncorrected and recorded as obtained on a Thomas-Hoover capillary melting point apparatus; NMR spectra were determined in $CDCl_3$ on a Varian A-60D spectrometer. Mass spectra were obtained with an Atlas MAT CH4 spectrometer. Analytical results for compounds followed by elemental symbols were within ±0.4% for those elements. The author is indebted to the Department of Physical and Analytical Chemistry Research of The Upjohn Company for those analyses.

**4-(3-Methanesulfonyloxypropyl)-4-phenylcyclohexan-1-one (3).** A solution of 15.81 g (0.048 mol) of the ester ketal in 160 ml of THF was added to a mixture of 2.0 g of $LiAlH_4$ in 20 ml of THF. The mixture was heated at reflux for 4 h and then cooled in ice. There was added in turn 2 ml of $H_2O$, 2 ml of 15% NaOH, and 6 ml of $H_2O$. The inorganic gel was collected on a filter and the filtrate taken to dryness. The product was obtained as a clear gum which showed a single spot on TLC.

To an ice-cold solution of the product from the previous reaction in 80 ml of pyridine there was added dropwise 16 ml of $CH_3SO_2Cl$. Following 17 h of standing in the cold, the mixture was poured into ice–$H_2O$. The precipitated gum was taken up in $C_6H_6$–$Et_2O$ and the organic layer washed in turn with $H_2O$, ice-cold 2.5 N HCl, $H_2O$, $NaHCO_3$, and brine. The residue which remained when the extract was taken to dryness was chromatographed on 1.5 l. of silica gel (elution with 10% EtOAc–$CH_2Cl_2$). Those fractions which showed the same single spot on TLC were combined to afford 14.95 g (88%) of product as a gum.

A solution of 14.95 g (0.042 mol) of the ketal and 30 ml of 2.5 N HCl in 150 ml of $Me_2CO$ was stirred at room temperature for 48 h. There was then added 20 ml of saturated $NaHCO_3$ and the bulk of the solvent removed in vacuo. The residue was treated with $CH_2Cl_2$. The organic layer was separated, washed with $NaHCO_3$, $H_2O$, and brine, and taken to dryness. The residual solid was recrystallized from $Me_2CO$–SSB[5] to give 10.07 g (77%) of ketone: mp 103–105 °C; $m/e^+$ 310. Anal. ($C_{16}H_{22}O_4S$) C, H.

**5-Phenylbicyclo[3.3.1]nonan-2-one (4).** To a mechanically stirred solution of 18.74 g (0.060 mol) of the mesylate in 185 ml of THF there was added all at once 6.75 g of *t*-BuOK. At the end of 2 h of stirring 50 ml of $H_2O$ was added followed by $Et_2O$ and $C_6H_6$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was chromatographed on 1.2 l. of silica gel (elution with $CH_2Cl_2$). The crystalline fractions were combined to give 10.0 g (78%) of product, mp 63–65 °C.

The analytical sample, mp 73–75 °C, was obtained by recrystallization from SSB (cooling in freezer): $m/e^+$ 214. Anal. ($C_{15}H_{16}O$) C, H.

***endo*-5-Phenylbicyclo[3.3.1]nonan-2-ol (5).** A solution of 2.47 g (0.0012 mol) of the ketone and 0.44 g of $NaBH_4$ in 50 ml of *i*-PrOH was stirred at room temperature for 4 h. The bulk of the solvent was removed in vacuo and the residue diluted with $H_2O$. The precipitated solid was collected on a filter and recrystallized from SSB. There was obtained 2.18 g (88%) of product: mp 77–79 °C; $m/e^+$ 216. Anal. ($C_{15}H_2O$) C, H.

***exo*-5-Phenylbicyclo[3.3.1]nonyl-2-amine Hydrochloride (8).** The alcohol 5 (2.18 g, 1 mmol) in 22 ml of pyridine was treated with 2.2 ml of $CH_3SO_2Cl$. The product was worked up as in the mesylate reaction above to afford an amorphous gum.

A mixture of the crude mesylate from the previous experiment and 2.5 g of $NaN_3$ in 25 ml of DMF was stirred for 17 h in an oil bath at 90 °C. The solvent was then removed under oil pump vacuum and the residue diluted with $H_2O$ and $C_6H_6$. The organic layer was washed with $H_2O$ and brine and taken to dryness.

A solution of the crude azide in 60 ml of THF was added to 0.40 g of $LiAlH_4$ in 10 ml of THF. Following 6 h of stirring, the mixture was cooled in ice and treated in turn with 0.4 ml of $H_2O$, 0.4 ml of 15% NaOH, and 1.2 ml of $H_2O$. The inorganic gel was collected on a filter and the filtrate taken to dryness. A solution of the residue in $Et_2O$ was treated with HCl in $Et_2O$. The precipitated solid was recrystallized from MeOH–EtOAc to give 1.38 g (55% based on alcohol) of product: mp 212–214 °C; $m/e^+$ 215. Anal. ($C_{15}H_{22}ClN$) C, H, N.

***exo*-4′-Fluoro-4-(5-phenylbicyclo[3.3.1]non-2-ylamino)-butyrophenone Hydrochloride (9).** A mixture of the free base from 1.38 g (0.0058 mol) of the amine HCl, 1.10 g of KI, 1.71 g of $K_2CO_3$, and 1.59 g of the neopentyl glycol ketal of 4′-chloro-*p*-fluorobutyrophenone in 30 ml of DMF was heated at 90 °C for 15 h. The solvent was then removed in vacuo and the residue diluted with $H_2O$ and $C_6H_6$. The organic layer was washed with $H_2O$ and brine and taken to dryness. A solution of the residue and 8 ml of 2.5 N HCl in 20 ml of MeOH was stirred at room temperature for 4 h. The bulk of the solvent was removed in vacuo. The residue was washed with $Et_2O$ and then extracted with $CH_2Cl_2$. The residue which remained when this last extract was taken to dryness was recrystallized twice from $CH_3CN$. There was obtained 0.80 g (35%) of product: mp 166–169 °C. Anal. ($C_{25}H_{31}ClFNO$) C, H, N.

**5-Phenylbicyclo[3.3.1]nonan-2-one Oxime (10).** A mixture of 10.0 g (0.046 mol) of the ketone, 10.0 g of $NH_2OH$·HCl, and 15 ml of 50% NaOH in 100 ml of $H_2O$ and 200 ml of THF was

stirred at reflux for 7 h. The bulk of the solvent was then removed in vacuo and the residue acidified with dry ice. The precipitate was taken up in $Et_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was recrystallized from $Et_2O$–SSB containing a few drops $H_2O$ to give 8.55 g (81%) of product: mp 98–100 °C; $m/e^+$ 229. Anal. ($C_{15}H_{19}NO$) C, H, N.

*endo*-**5-Phenylbicyclo[3.3.1]nonyl-2-amine Hydrochloride (12).** A solution of 4.0 g (0.0175 mol) of the oxime and 8 ml of $Ac_2O$ in 20 ml of pyridine was allowed to stand at room temperature for 5 h. The mixture was then poured into ice–$H_2O$ and the precipitate taken up in $Et_2O$–$C_6H_6$. The organic layer was washed in turn with $H_2O$, ice-cold 2.5 N HCl, $H_2O$, and brine and taken to dryness. The NMR of the residue was in agreement with the structure.

To an ice-cooled solution of the residue in 50 ml of THF there was added 25 ml of 1 N $B_2H_6$ in THF. Following 17 h of standing in the cold 1 ml of $H_2O$ was added dropwise and the bulk of the solvent removed in vacuo. The residue was stirred with 100 ml of 2.5 N HCl covered with $Et_2O$. At the end of 3 h the mixture was made strongly basic and extracted with $Et_2O$. This extract was washed with $H_2O$ and brine and taken to dryness. The residue was dissolved in a small amount of $Et_2O$ and treated with HCl in $Et_2O$. The precipitated solid was recrystallized twice from MeOH–EtOAc to give 1.30 g (30%) of product: mp 290–295 °C; $m/e^+$ 215. Anal. ($C_{15}H_{22}ClN$) H, N; C, calcd, 71.54; found, 72.13.

*endo*-**4′-Fluoro-4-(5-phenylbicyclo[3.3.1]non-2-ylamino)-butyrophenone Hydrochloride (13).** A mixture of the free base from 1.30 g (0.0052 mol) of the HCl salt, 1.04 g of KI, 1.61 g of $K_2CO_3$, and 1.50 g of the neopentylglycol ketal of 4′-chloro-*p*-fluorobutyrophenone in 30 ml of DMF was stirred for 17 h at 90 °C. The solvent was then removed in vacuo and the residue diluted with $H_2O$ and $C_6H_6$. The organic layer was washed with $H_2O$ and brine and taken to dryness.

A solution of the residue in 5 ml of 2.5 N HCl and 10 ml of MeOH was stirred at room temperature for 3 h. The bulk of the solvent was removed in vacuo. The residue was washed with $Et_2O$ and then extracted with $CH_2Cl_2$. This last extract was taken to dryness and the residue recrystallized twice from $CH_2Cl_2$–$Me_2CO$. There was obtained 0.68 g (27%) of product: mp 197–198 °C. Anal. ($C_{25}H_{31}ClFNO$) C, H, N.

**Acknowledgment.** The author wishes to express his indebtedness to Dr. A. D. Rudzik of these laboratories for making available the biological testing results.

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# Synthesis of Cephalosporin-4-aldehydes[1]

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The first reported synthesis of cephalosporin-4-aldehyde derivatives has been achieved via Moffatt oxidation of the corresponding 4-hydroxymethylcephalosporins. The aldehyde 1 was converted into a number of polar derivatives, in particular the acrylic acid derivative 13 which is the 4-vinylogue of sodium cephalothin. None of the new cephalosporin derivatives possessed useful antibacterial activity.

Although the synthesis of the penicillin-3-aldehyde system was achieved a number of years ago,[2] the corresponding cephalosporin-4-aldehyde system has not to date been described. In connection[3,4] with work involving total synthesis of cephalosporin antibiotics carried out in our laboratories, a convenient synthesis of 3-acetoxymethyl-7β-[2-(2-thienyl)acetamido]ceph-3-em-4-carboxaldehyde (1) was required, and we now report the achievement of this objective. In addition, with the ceph-3-em-4-carboxaldehyde system available, we were able to prepare a number of new cephalosporin derivatives in which the carboxylic acid function is replaced by other polar groups.

**Chemistry.** It was felt that on account of the α,β-unsaturation present in ceph-3-em derivatives, the chemistry involved would not necessarily parallel that previously described[2] for the penam system. As there are a large number of methods available for the oxidation of primary alcohols to the corresponding aldehydes, the known alcohol 2[5] was selected for study.

Initial attempts at oxidizing the alcohol 2 to the corresponding aldehyde 1 using a number of standard procedures were discouraging. Since it was suspected that sensitivity of the desired aldehyde 1 was the problem, the alcohol 9 was prepared via *m*-chloroperbenzoic acid treatment of the alcohol 2 with the hope that the corresponding aldehyde 10 would be more easily handled. This indeed turned out to be the case, when application of the particularly mild Moffatt oxidation[6] to the alcohol 9 led to the aldehyde 10 in 80% yield.

When similar conditions were applied to the alcohol 2, the reaction appeared to have proceeded (precipitation of dicyclohexylurea, darkening of color), but the desired aldehyde 1 could not be isolated from the crude product using chromatography. Examination of the crude product using NMR showed that it was essentially a mixture of the aldehyde 1 and dicyclohexylurea. The problem of isolating 1 was solved by treating the crude product with EtOH and *p*-TsOH and chromatographing the resulting material on silica gel to give the diethyl acetal 3 (62% yield based on 2). Similarly, treatment of the crude aldehyde in THF solution with ethylene glycol and *p*-TsOH afforded the ethylene acetal 4 (45% yield based on 2).

Conversion of the acetal 3 to the aldehyde 1 was readily achieved by exposing 3 in dioxane to dilute hydrochloric acid, whereupon the aldehyde 1 was obtained in 45% yield. The oxime 5, methoxime 6, semicarbazone 7, and carboxymethoxime 8 derivatives of 1 were readily prepared by reacting the aldehyde briefly with an excess of the appropriate reagent.

Upon treatment with diphenylmethoxycarbonylmethylenetriphenylphosphorane, the aldehyde 1 afforded the olefin 11 in 40% yield. The trans configuration was assigned on account of the observed coupling constant of 15 Hz for the olefinic protons. Removal of the carboxyl protecting group of 11 afforded the acid 12 which was converted to the sodium salt (13) for biological evaluation.