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Ethynyl and Styryl Compounds of the Prodine Type

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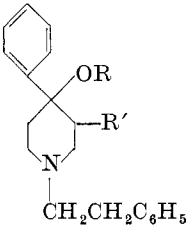
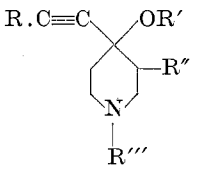
Compounds of type (I) (R = $COCH_3$ or COC_2H_5 and R′ = H or CH_3) are active analgesics in mice.[1] Beckett and co-workers[2–5] considered that the presence of a suitably orientated flat aromatic structure played an important role in the fit of an analgesic at a postulated receptor site. The analgesic drug-receptor was considered to depend, in part, upon the bonding between the aromatic ring of the drug and a complementary flat portion of the receptor by van der Waals' forces. Beckett *et al.*[6] have shown that replacement of the 4-phenyl group by pyridyl or thienyl groups in compounds of type (I) (where R = $COCH_3$ or COC_2H_5 and R′ = CH_3) results in a reduction of analgesic activity and this was attributed largely to the attendant increase in steric factors.



(I)



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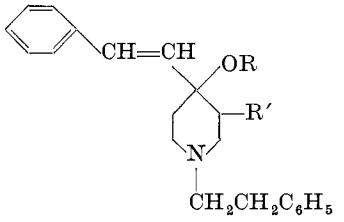

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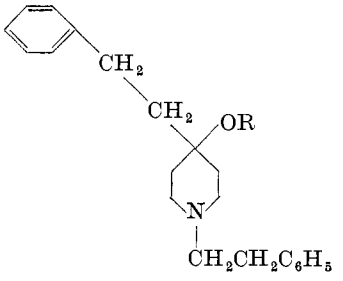

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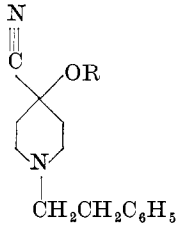
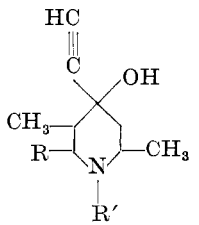


(V)

The importance of the phenyl grouping might be associated with its delocalized π electrons and the possible role which these might play in bonding with the receptor surface. To investigate whether the aromatic structure could be replaced by other groupings which, although non-aromatic, possess a π-cloud of electrons, compounds of the type (II) (R = H, CH_3 or C_4H_9; R′ = H, $COCH_3$ or COC_2H_5; R″ = H or CH_3 and R‴ = CH_3 or $CH_2CH_2 \cdot C_6H_5$) have been prepared and tested for 'analgesic activity' and other pharmacological effects.

The introduction of acetylenic linkages into potential analgesic-type molecules was of interest in view of reports that such groups increase the ease of absorption, stability and activity of a number of pharmacologically active compounds.[7–9] Compounds of type[5] (II) (R = C_6H_5, R′ = H, $COCH_3$ or COC_2H_5; R″ = H or CH_3 and R‴ = CH_3 or $CH_2CH_2C_6H_5$) and (III) (R = H, $COCH_3$ or COC_2H_5 and R′ = H) were also prepared and are of interest in that although the aromatic ring in the 4 position is shifted relative to the piperidine ring, the introduction of the ethynyl and styryl groupings would contribute to the electron availability around the 4-substituent. Compounds of type (IV) (R = H, $COCH_3$ or COC_2H_5) and (V) (R = H, $COCH_3$ or COC_2H_5) allowed the effect of replacing the 4-phenyl substituent by a phenethyl and C≡N grouping respectively to be investigated.

Nazarov *et al.*[10] prepared a series of *N*-substituted 2,5-dimethyl and 2,5,6-trimethyl-4-ethynyl-4-piperidinols (VI) (R = H, R′ = H, CH_3 or C_6H_5, and R = CH_3 and R′ = H, CH_3 or C_6H_5 respectively). The preparative method involved addition of



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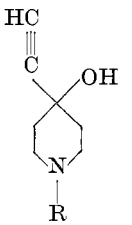


(VII)

potassium hydroxide to dry ether, saturation of the solution at −7° with acetylene, followed by addition of an ethanolic solution of the appropriate piperidone. During the course of the present

investigation, Da Re,[11] using a similar method, prepared *N*-substituted 4-ethynyl-4-piperidinols of the type (VII) (R = CH_3, C_2H_5, C_4H_9 C_5H_{11}, C_6H_5 or $CH_2 \cdot C_2H_5$). Attempts to prepare compounds of type (II) using the method of Nazarov *et al.*[10] were unsuccessful in our hands and a method similar to that used by Hennion and O'Shea[12] for the preparation of 1-ethynyl-4-*t*-butylcyclohexanol was adopted. Acetylene or a substituted acetylene was passed into a stirred liquid ammonia suspension of sodamide (prepared *in situ*, ferric nitrate being used as catalyst), and after several hours an ethereal solution of the appropriate 4-piperidone was added. *N*-Phenethyl-3-methyl-4-phenylethynyl-4-piperidone was prepared by the addition of phenylacetylene to *N*-phenethyl-3-methyl-4-piperidone in the presence of sodamide in liquid ammonia, and also by the addition of the phenylacetylene Grignard to the ketone, but in each case only one of the two theoretically possible diastereoisomers could be isolated. As a result of investigations involving addition of phenylmagnesium bromide to *N*-substituted-2,5-dimethyl-4-piperidone, Nazarov *et al.*[13] suggested that the substituent on the nitrogen, by exerting a screening influence on the carbonyl group so that attack by the organometallic compound can take place from one side of the molecule only, exerts a profound effect on the proportion of isomers obtained. It is therefore of interest that addition of phenylacetylene to *N*-methyl-3-methyl-4-piperidone gave two isomers of *N*-methyl-3-methyl-4-phenylethynyl-4-piperidinol, the alcohols being separated by fractional crystallization of their acetoxy esters.

1-Bromoethynyl-cyclohexanol[14] has been shown to possess hypnotic activity and consequently *N*-phenethyl-4-bromoethynyl-4-piperidinol was prepared by treating *N*-phenethyl-4-ethynyl-4-piperidinol with a solution of sodium hypobromite according to the method of Di Paco and Tauro.[15] *N*-Phenethyl-3-methyl-4-chloro-4-phenylethynylpiperidine was prepared by treating the corresponding acetylenic piperidinol with thionyl chloride following the method of Archer *et al.*[16] The acetylenic piperidinols were converted to their esters by refluxing with acid anhydride in the presence of pyridine.

N-Phenethyl-4-phenylethynyl-4-piperidinol was reduced with lithium aluminium hydride in tetrahydrofuran to give an almost

quantitative yield of *trans*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer A), while reduction with sodium in liquid ammonia gave *N*-phenethyl-4-phenethyl-4-piperidinol, possibly owing to the conjugation of the molecule in the olefinic state causing the alkene bond to be further reduced to the saturated state.[17] *N*-Phenethyl-4-phenylethynyl-4-piperidinol was hydrogenated using Lindlar catalyst[18] to give *cis*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer B). Hydrogenation of an ethereal solution of 4-phenethyl-4-phenylethynyl-4-piperidinol using 5 per cent palladized calcium carbonate gave a mixture of the starting material, *N*-phenethyl-4-phenethyl-4-piperidinol and *cis*-*N*-phenethyl-4-styryl-4-piperidinol. A change of solvent to ethanol, however, resulted in the exclusive formation of *N*-phenethyl-4-phenethyl-4-piperidinol. The latter was also obtained when hydrogenation was carried out using 5 per cent palladized charcoal.

The configurations assigned to the isomers of *N*-phenethyl-4-styryl-4-piperidinol on the basis of the preparative methods were confirmed by ultraviolet absorption evidence. Both isomers gave a styrene-type peak in the 245 mμ region, the *trans* isomer (base) having ϵ 21,193 at λ_{max} 251 mμ, while the *cis* (hydrochloride) has ϵ 9,747 at λ_{max} 245 mμ.

Catalin-type atomic models of the *cis* and *trans* isomers showed that owing to steric hindrance the *cis* isomer was much less planar than the *trans* and it was not surprising that the intensity of absorption of the *cis* isomer was approximately half that of the *trans* in the 245 mμ region.

The *cis* and *trans* styryl piperidinols were esterified by the lithium salt method,[19] the *trans*-acetoxy ester hydrochloride having ϵ 20,860 at λ_{max} 252 mμ and the *cis* hydrochloride ϵ 8,782 at λ_{max} 238 mμ, which was further confirmation of the assigned configurations. Attempts to prepare the acetoxy esters of the *cis* and *trans* styryl piperidinols by refluxing with anhydride and pyridine gave in each case an identical eliminated compound, *N*-phenethyl-4-styryl-1,2,5,6-tetrahydropyridine.

The infra-red spectra of the *cis*- and *trans*-styryl-piperidinols showed that both isomers absorbed in the 990–965 cm^{-1} and 690 cm^{-1} regions; at the former the *cis* isomer had the stronger absorption, while in the 690 cm^{-1} region the reverse was the case. As a general rule *trans* isomers absorb more strongly in the 990-

965 cm^{-1} region than *cis* isomers, the reverse being the case in the 690 cm^{-1} region,[20] a generalization based on data obtained with relatively simple ethylenic compounds. It is not unlikely that in the case of the compounds under discussion the absorption would be influenced by the adjacent aromatic groupings.

Addition of phenethylmagnesium bromide to *N*-phenethyl-3-methyl-4-piperidone gave a low yield (9 per cent) of *N*-phenethyl-3-methyl-4-phenethyl-4-piperidinol which was identical with the compound prepared by the reduction of *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol. Nazarov *et al.*[21] found that 1,2,5-trimethyl-4-vinylethynyl-4-piperidinol (prepared by addition of the corresponding piperidone to an ethereal solution of potassium hydroxide saturated with vinylacetylene) on reduction to the 4-butyl-piperidinol gave a different isomer to that obtained from the Grignard addition of 1-chlorobutane to 1, 2, 5-trimethyl-4-piperidone.

When the Grignard addition of phenethyl magnesium bromide to *N*-methyl-3-methyl-4-piperidone was attempted, only unchanged piperidone was obtained.

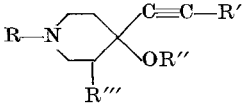
Pharmacological Testing

The acetylenic and styryl piperidinols and their esters were tested for 'analgesic activity' by subcutaneous injection in mice, an adaption of the hot-plate method as described by Janssen and Jagenau[22] being employed. The ED_{50} values (mg/kg) are shown in Table I. The compounds were also tested for mydriatic activity in mice as described by Janssen and his co-workers[23–25] and in no case was significant mydriatic activity noted (see Table I). Since Janssen and Jagenau[22, 26] have shown that in many morphine-like analgesics there is a significant positive correlation between analgesic activity and mydriatic activity in mice, it is therefore assumed that the pharmacological effect indicated by the hot-plate test results primarily from a general central nervous depression rather than morphine-like analgesia.

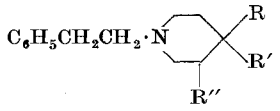
Of the acetylenic piperidinols tested, only one, *N*-phenethyl-4-phenylethynyl-4-piperidinol (ED_{50} 18·2 mg/kg) (No. 4)* showed pronounced pharmacological activity. When it was tested for

* Numbers refer to compounds in Table I.

Table I. Pharmacological activities of *N*-substituted-4-acetylenic-4-piperidinols and related compounds[a]



No.	R	R′	R″	R‴	Hot plate test ED_{50}, mg/kg	Mydriatic activity ED_{50}, mg/kg	'Analgesic activity' (Tail-pinch method)
1	$C_6H_5(CH_2)_2$[b]	H	H	H	>40	>40	−ve at 150 mg/kg
2	$C_6H_5(CH_2)_2$[b]	CH_3	H	H	>40	>40	+ve at 150 mg/kg
3	$C_6H_5(CH_2)_2$[b]	$CH_3(CH_2)_3$	H	H	34	>40	
4	$C_6H_5(CH_2)_2$[b]	C_6H_5	H	H	18·2	>40	ED_{50} 10·7 mg/kg
5	$C_6H_5CH_2$	C_6H_5	H	H	>40	>40	ED_{50} 80 mg/kg
6	$C_6H_5(CH_2)_2$	C_6H_5	H	CH_3	>40	>40	−ve at 100 mg/kg
7	$C_6H_5(CH_2)_2$	H	$COCH_3$	H	>40	>40	−ve at 150 mg/kg
8	$C_6H_5(CH_2)_2$	H	COC_2H_5	H	>40	>40	
9	$C_6H_5(CH_2)_2$	CH_3	$COCH_3$	H	>40	>40	
10	$C_6H_5(CH_2)_2$	CH_3	COC_2H_5	H	>40	>40	
11	$C_6H_5(CH_2)_2$	$CH_3(CH_2)_3$	$COCH_3$	H	>40	>40	
12	$C_6H_5(CH_2)_2$[c]	$CH_3(CH_2)_3$	COC_2H_5	H	>20	>20	
13	$C_6H_5(CH_2)_2$	C_6H_5	$COCH_3$	H	>40	>40	−ve at 400 mg/kg
14	$C_6H_5(CH_2)_2$	C_6H_5	COC_2H_5	H	47	40	
15	$C_6H_5CH_2$	C_6H_5	$COCH_3$	H	>40	>40	
16	$C_6H_5(CH_2)_2$	C_6H_5	$COCH_3$	CH_3	>40	>40	−ve at 200 mg/kg
17	$C_6H_5(CH_2)_2$	C_6H_5	COC_2H_5	CH_3	>40	>40	
18	CH_3[d]	C_6H_5	$COCH_3$	CH_3	>40	>40	
19	CH_3[d]	C_6H_5	$COCH_3$	CH_3	>40	>40	
20	$C_6H_5(CH_2)_2$	Br	H	H			−ve at 100 mg/kg

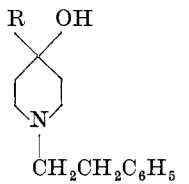


	R	R′	R″			
21	CH═CH·C_6H_5 (*trans*)	OH	H			−ve at 100 mg/kg
22	CH═CH·C_6H_5 (*cis*)	OH	H	>40	>40	
23	CH═CH·C_6H_5 (*trans*)	$OCOCH_3$	H			−ve at 100 mg/kg
24	CH═CH·C_6H_5 (*cis*)	$OCOCH_3$	H			Sl. + at 100 mg/kg
25	$C_6H_5CH_2CH_2$[b]	OH	H	22	>40	
26	$C_6H_5CH_2CH_2$	$OCOCH_3$	H	18	>40	
27	$CH_2CH_2C_6H_5$[b]	OH	CH_3	24	>40	
28	C≡N[b]	OH	H	>40	>40	Sl. +ve at 25 mg/kg
29	C≡N	$OCOCH_3$	H	24	>40	+at 40 mg/kg
30	C≡N[b]	$OCOC_2H_5$	H	>40	>40	
31	C≡C.C_6H_5	Cl	CH_3	>40	>40	−ve at 50 mg/kg
32[e]	C_6H_5	OH	H	34	36·5[f]	
33	C_6H_5	$OCOCH_3$	H	3·3	3·0[f]	
34	C_6H_5	$OCOC_2H_5$	H	3·8	5·0[f]	
35	$C_6H_5CH_2$	OH	H	30	>40[f]	
36	$C_6H_5CH_2$	$OCOCH_3$	H	>40	>40[f]	
37	$C_6H_5CH_2$	$OCOC_2H_5$	H	>40	>40[f]	
38	Morphine HCl			12	13[g]	
39	Pethidine HCl			28	21·5[g]	
40	$C_6H_5CH_2CH_2$·N⟨ ⟩CH═CH·C_6H_5					−ve at 100 mg/kg

[a] Compounds were tested in the form of hydrochlorides except where otherwise stated.
[b] Free base.
[c] Hydrobromide.
[d] Hydroiodide.
[e] Compounds Nos. 32–39 included for comparison.
[f] References 1 and 28.
[g] Reference 22.

'analgesic activity' in mice by the Haffner tail-pinch method as modified by Bianchi and Franceschini[27] and David, Leith-Ross and Vallance,[28] the ED_{50} by the subcutaneous route was 10 mg/kg compared with 8 mg/kg for pethidine hydrochloride.

As assessed by the hot-plate method, *N*-phenethyl-4-phenylethynyl-4-piperidinol (VIII) (R = $C{\equiv}C{\cdot}C_6H_5$) (No. 4) is pharmacologically more active than the corresponding *N*-phenethyl-4-phenyl-4-piperidinol (VIII) (R = C_6H_5) ED_{50} 34 mg/kg (No. 32) and *N*-phenethyl-4-benzyl-4-piperidinol[29] (VIII) (R = $CH_2C_6H_5$) ED_{50} 30 mg/kg (No. 35).



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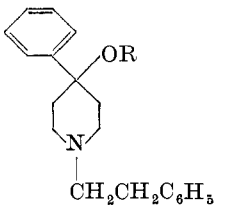


(IX)

Replacement of the 4-phenyl substituent by an ethynyl- or alkyl-substituted ethynyl group does not result in an increase in central nervous activity in mice since the ethynyl and alkyl ethynyl derivatives were virtually without activity (compare compounds 1, 2, 3 and 32). The replacement of the 4-phenyl substituent in a potent analgesic such as (IX) (R = $COCH_3$ or COC_2H_5) (Nos. 33 and 34) by an ethynyl or substituted ethynyl group results in a complete loss of morphine-like analgesic activity (compare compounds 33 and 34 with Nos. 7, 9, 13 and 14).

Reduction of *N*-phenethyl-4-phenylethynyl-4-piperidinol to the *cis*- and *trans*-styryl analogues (VIII) (R = $CH{=}CH{\cdot}C_6H_5$) (Nos. 21 and 22) appeared to result in a loss of the central nervous effect (the *cis*-styryl-piperidinol having $ED_{50} > 40$ mg/kg). Complete reduction to the *N*-phenethyl-4-phenethyl-4-piperidinol, however, (VIII) (R = $CH_2CH_2C_6H_5$), ED_{50} 22 mg/kg, (No. 25) gave a compound with comparable activity.

It is also clear that the pharmacological activity was lost on replacing the 4-phenylethynyl group by a $C{\equiv}N$ group (VIII) (R = CN) (cf. compounds 4 and 28).

In direct contradistinction to *N*-phenethyl-4-phenyl-4-piperidinol, the esters of which are potent morphine-like analgesics

(acetoxy, ED_{50} 3·3 mg/kg; propionoxy, ED_{50} 3·8 mg/kg,[1] Nos. 33 and 34), the esters of the 4-phenethynyl compound (VIII) (R = $C{\equiv}C \cdot C_6H_5$) (Nos. 7 and 8) were devoid of activity. The acetoxy ester of *N*-phenethyl-4-phenethyl-4-piperidinol (No. 26), however, had an activity which was about the same as, or slightly higher than, that of the parent piperidinol.

While conversion of the *N*-phenethyl-4-cyano-4-piperidinol (VIII) (R = CN) to its acetoxy ester (No. 29) gave a compound with pronounced central nervous activity, the propionoxy ester (No. 30) was devoid of activity.

With the acetylenic piperidinols, substitution in the 3-position did not result in an increase in activity, indeed the *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol (No. 6) was devoid of activity (cf. analgesics of the reversed esters of pethidine-type in which substitution enhances the analgesic effect[1, 30]). On the other hand 3-methyl substitution of *N*-phenethyl-4-phenethyl-4-piperidinol (No. 27) gave a compound comparable in activity to the unsubstituted piperidinols.

A number of the compounds were also tested for analgesic activity by the tail-pinch method, and the results are shown in Table I. With the exception of *N*-phenethyl-4-phenylethynyl-4-piperidinol none showed significant analgesic activity.

From a consideration of the hot-plate activities, it is clear that replacement of the 4-phenyl substituent in a potent morphine-like analgesic such as (IX) (R = $COCH_3$ or COC_2H_5) by a non-aromatic grouping such as an ethynyl or substituted ethynyl (which have π electron clouds) results in a complete loss of morphine-like analgesic activity. From the evidence available it would appear that the 4-phenyl substituent is necessary and that its bonding capacity with an analgesic receptor site cannot be replaced by that of another group, simply because this group has a π electron cloud. On the other hand the general central nervous activity of the piperidinols increases when the 4-phenyl group is replaced by a phenylethynyl or phenethyl group.

Compounds 1–2, 4–7, 13, 16, 20–22, 24, 28–31 and 40 were subjected to a screening programme the object of which was to assess their central nervous system activities. The screening procedure included dose range and toxicity studies and tests for anti-amphetamine, anti-histamine, anti-Tremorine, maximal

pentylenetetrazol seizure, maximal electroshock seizure, conditioned response, and parasympatholytic and sympathetic block.

Although a number of the compounds showed some activity in some of these tests the results were such as not to merit further pharmacological investigation.

Experimental

Acetylenic Piperidinols

(*a*) The following method for the preparation of N-*phenethyl-4-ethynyl-4-piperidinol* was typical of the preparative methods used. Acetone-free acetylene was bubbled for 4 h through a stirred, cooled (−25°) suspension of sodamide prepared from sodium (4·1 g) and liquid ammonia (750 ml) to which a crystal of ferric nitrate had been added. A solution of *N*-phenethyl-4-piperidone (30·3 g) in ether (150 ml) was added dropwise over a period of 1 h. The passage of acetylene through the stirred and cooled solution was continued for a further 6 h, ether (25 ml) being added every 2 h. Ammonium chloride (7·5 g) was added in small portions, followed by concentrated ammonium hydroxide solution (50 ml) and crushed ice (100 g), and the mixture was kept at room temperature overnight. The residue was extracted with chloroform (3 × 150 ml), the combined chloroform solutions were extracted with dilute hydrochloric acid (3 × 100 ml), and the acidic solution was washed with ether, made alkaline with ammonium hydroxide solution and extracted with chloroform (3 × 100 ml). The combined chloroform extracts were evaporated to give a solid residue which crystallized from benzene–petroleum ether (40–60°) to give *N*-phenethyl-4-ethynyl-4-piperidinol, m.p. 96·5–97·5°. In the cases of the butylethynyl and phenylethynyl analogues the acetylenic intermediates were added in the form of an ethereal solution. *n*-Butyl-acetylene was prepared according to the method described by Vogel.[31]

(*b*) N-*Phenethyl-3-methyl-4-phenylethynyl-4-piperidinol.* (1) Sodamide prepared from sodium (4·3 g) and liquid ammonia (750 ml) was reacted with phenylacetylene (24 g) and *N*-phenethyl-3-methyl-4-piperidone (22 g) by the method previously described. The product, a dark green semi-solid (28·6 g) was crystallized after considerable difficulty from benzene–petroleum ether (40–60°) to

give *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol, m.p. 144·5° (10·4 g). All attempts to isolate a second isomer from the mother liquors failed, intractable tarry residues being obtained.

(2) In a repeat experiment, the dark green semi-solid (33 g) was dissolved in a solution of 5 per cent v/v benzene in petroleum ether (60–80°) and the solution chromatographed on an alumina column using a progressively stronger solution of benzene in petroleum ether as eluant. A total of 29·7 g (90 per cent) of the material was recovered, of which 9·12 g (28 per cent) on crystallization from benzene–petroleum ether (40–60°) gave *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol, m.p. and mixed m.p. 144·5°. The remainder of the material (20·66 g) was obtained as a viscous oil which could not be solidified or crystallized and from which a crystalline derivative could not be obtained. The oil on analysis gave C, 81·9; H, 8·4; N, 4·4; equiv. wt. 316. *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol, $C_{22}H_{25}NO$, requires C, 82·7; H, 7·9; N, 4·4; equiv. wt. 319, and it appeared that the oil was the other isomer or a mixture of isomers. An attempt to distil this oil failed.

(3) Sodium (4·3 g) was added to a solution of phenylacetylene (28·5 g) in ether (280 ml) and the mixture stirred for 8 h at room temperature. A solution of *N*-phenethyl-3-methyl-4-piperidone (37·5 g) in ether (200 ml) was added dropwise and the resulting mixture stirred for 12 h and then decomposed by adding crushed ice and dilute hydrochloric acid (100 ml). The aqueous layer was separated, made alkaline with concentrated ammonium hydroxide solution, and extracted with chloroform (3 × 100 ml). Evaporation of the chloroform extracts gave a viscous oil (41·8 g) which solidified after storage for 72 h in a vacuum desiccator. The solid obtained was very hygroscopic and could not be crystallized. Attempts to prepare crystalline derivatives failed.

(4) Phenylacetylene (30·6 g) in ether (100 ml) was added dropwise to a stirred ethereal solution of ethylmagnesium bromide prepared from ethyl bromide (32·7 g) and magnesium (7·2 g). The mixture was stirred for 12 h and *N*-phenethyl-3-methyl-4-piperidone (33 g) in ether (100 ml) was added dropwise; the stirring was then continued for a further 24 h and the mixture was decomposed with crushed ice and dilute hydrochloric acid (150 ml). The aqueous layer was washed with ether, and the free base was

liberated with concentrated ammonium hydroxide solution and extracted with benzene (3 × 150 ml). The combined benzene extracts on evaporation gave a solid residue (27·4 g) which crystallized from benzene–petroleum ether (40–60°) to give *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol, m.p. and mixed m.p. 144·5° (25·6 g). A thorough investigation of the mother liquor failed to give a second isomer.

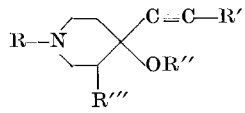
(*c*) N-*Methyl-3-methyl-4-phenylethynyl-4-piperidinol.* This was prepared from sodium (8·9 g), liquid ammonia (1500 ml), phenylacetylene (48 g) and *N*-methyl-3-methyl-4-piperidone (25·2 g) by the general method. Crystallization of the reaction product from benzene–petroleum ether (40–60°) gave a mixture of the isomers of *N*-methyl-3-methyl-4-phenylethynyl-4-piperidinol, m.p. 88–94° (36·8 g). A solution of this solid (19 g) in benzene (75 ml) was added dropwise to a stirred cooled ethereal solution of phenyllithium prepared from lithium (1·34 g) and bromobenzene (16·5 g). The mixture was refluxed for 0·5 h and cooled in an ice-bath; acetic anhydride (9·4 g) was added, and the resultant suspension was stirred overnight. The product was decomposed with crushed ice and acetic acid (20 ml), the acidic layer was separated, made alkaline with concentrated ammonium hydroxide solution and extracted with ether, and the combined ethereal extracts were evaporated to give an oil which on treatment with hydriodic acid gave a solid (22·8 g). This solid on fractional crystallization gave *N*-methyl-3-methyl-4-acetoxy-4-phenylethynylpiperidine hydriodide in two isomeric forms: Isomer A, m.p. 213° (d.) (6·6 g), and Isomer B, m.p. 186·5–187·5° (12·3 g).

A mixture of Isomer A (2·2 g), potassium hydroxide (0·8 g) and ethanol (95 per cent, 30 ml) was refluxed for 20 h. The residue obtained on evaporation was dissolved in water and extracted with chloroform (3 × 25 ml) which on evaporation gave *N*-methyl-3-methyl-4-phenylethynyl-4-piperidinol (Isomer A), m.p. 133° (1·1 g), as needles from benzene–petroleum ether (40–60°).

In the same way the isomeric ester (B) (1·8 g) gave *N*-methyl-3-methyl-4-phenylethynyl-4-piperidinol (Isomer B), m.p. 96–97° (1·0 g), as rosettes of needle crystals from benzene–petroleum ether (40–60°).

The acetylenic piperidinols prepared are listed in Table II, along with analytical data.

Table II. N-Substituted-4-acetylenic-4-piperidinols and their esters



R	R′	R″	R‴	Formula	Base m.p.	Salt m.p.	Analysis, % Calcd. C	H	N	Halogen	Equiv. wt.	Found C	H	N	Halogen	Equiv. wt.	Solvent[a]
$C_6H_5CH_2CH_2$	H	H	H	$C_{15}H_{19}NO$	96·5–97·5°		78·6	8·4	6·1		229	79·7	8·5	6·0		230	A
$C_6H_5CH_2CH_2$	CH_3	H	H	$C_{16}H_{21}NO$	99°		79·0	8·7	5·8		243	79·8	8·7	5·9		243	C
$C_6H_5CH_2CH_2$	CH_3	H	H	$C_{16}H_{22}ClNO$		HCl 197°	68·7	7·9	5·0		280	68·8	7·6	5·3		277	B
$C_6H_5CH_2CH_2$	$CH_3(CH_2)_3$	H	H	$C_{19}H_{27}NO$	80°		80·0	9·5	4·9		285	79·6	9·4	5·0		286	D
$C_6H_5CH_2CH_2$	C_6H_5	H	H	$C_{24}H_{23}NO$	151·5°		82·6	7·6	4·6		305	82·6	7·4	4·4		303	C_6H_6
$C_6H_5CH_2CH_2$	C_6H_5	H	H	$C_{21}H_{24}ClNO$		HCl 180°	73·8	7·1	4·1	10·4	342	73·2	6·8	4·0	10·3	340	B
$C_6H_5CH_2$	C_6H_5	H	H	$C_{20}H_{22}ClNO$		HCl 187°	73·3	6·8	4·3	10·8	328	73·4	6·6	4·3	10·9	330	B
$C_6H_5CH_2CH_2$	C_6H_5	H	CH_3	$C_{22}H_{25}NO$	144·5°		82·7	7·9	4·4		319	82·8	7·9	4·4		320	A
CH_3 (Isomer A)	C_6H_5	H	CH_3	$C_{15}H_{19}NO$	133°		78·6	8·4	6·1		229	78·7	8·3	6·2		227	A
CH_3 (Isomer B)	C_6H_5	H	CH_3	$C_{15}H_{19}NO$	96–97°		78·6	8·4	6·1		229	78·8	8·2	6·4		228	A
$C_6H_5CH_2CH_2$	H	$COCH_3$	H	$C_{17}H_{22}ClNO_2$		HCl 255°	66·3	7·2	4·6	11·5	308	66·2	7·1	4·4	11·4	306	B
$C_6H_5CH_2CH_2$	H	COC_2H_5	H	$C_{18}H_{24}ClNO_2$		HCl 238·5°	67·2	7·5	4·4	11·0	322	67·7	7·4	4·6	10·8	321	C_2H_5OH
$C_6H_5CH_2CH_2$	CH_3	$COCH_3$	H	$C_{18}H_{24}ClNO_2$		HCl 241°	67·2	7·5	4·4		322	67·0	7·7	4·3		319	B
$C_6H_5CH_2CH_2$	CH_3	COC_2H_5	H	$C_{19}H_{26}ClNO_2$		HCl 239°	67·9	7·8	4·2		336	67·7	7·5	4·2		333	C_2H_5OH
$C_6H_5CH_2CH_2$	$(CH_2)_3CH_3$	$COCH_3$	H	$C_{21}H_{29}ClNO_2$		HCl 204–205°	69·3	8·4	3·9		364	68·9	8·2	4·0		360	E
$C_6H_5CH_2CH_2$	$CH_3(CH_2)_3$	COC_2H_6	H	$C_{22}H_{32}BrNO_2$		HBr 205°	62·5	7·6	3·3		423	62·2	7·7	3·3		424	E
$C_6H_5CH_2CH_2$	C_6H_5	$COCH_3$	H	$C_{23}H_{24}ClNO_2$		HCl 239°	71·9	6·8	3·7	9·2	384	72·3	6·8	3·6	9·4	385	C_2H_5OH
$C_6H_5CH_2CH_2$	C_6H_5	COC_2H_5	H	$C_{24}H_{28}ClNO_2$		HCl 215°	72·4	7·1	3·5		398	72·2	7·0	3·6		399	B
$C_6H_5CH_2$	C_6H_5	$COCH_3$	H	$C_{22}H_{24}ClNO_2$		HCl 234°	71·4	6·6	3·8		370	71·4	6·4	3·7		372	C_2H_5OH
$C_6H_5CH_2CH_2$	C_6H_5	$COCH_3$	CH_3	$C_{24}H_{28}ClNO_2$		HCl 236°	72·4	7·1	3·5		398	71·9	7·0	3·3		399	B
$C_6H_6CH_2CH_2$	C_6H_5	COC_2H_5	CH_3	$C_{25}H_{30}ClNO_2$		HCl 201°	72·9	7·3	3·4		412	74·0	7·3	3·6		414	E
CH_3	C_6H_5	$COCH_3$	CH_3	$C_{17}H_{22}INO_2$ (Isomer A)		HI 213° (d)	51·5	5·6	3·5		399	50·3	5·3	3·6		402	B
CH_3	C_6H_5	$COCH_3$	CH_3	$C_{17}H_{22}INO_2$ (Isomer B)		HI 186·5–187·5°	51·5	5·6	3·5		399	51·7	5·9	3·3		397	B

[a] A: benzene–petroleum ether (40–60°); B: ethanol–ether; C: petroleum ether (60–80°); D: petroleum ether (40–60°); E: isopropanol–ether.

N-Phenethyl-3-methyl-4-chloro-4-phenylethynyl-piperidone hydrochloride. A solution of thionyl chloride (6·5 g) in dry chloroform (25 ml) was added dropwise over a period of 0·5 h to a stirred, cooled (−15°) solution of *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol and the mixture refluxed for 3 h. On cooling and adding ether (25 ml) a solid was obtained which crystallized from ethanol to give *N*-phenethyl-3-methyl-4-chloro-4-phenylethynyl-piperidine hydrochloride, m.p. 199° (7·8 g).

Anal. Calcd. for $C_{22}H_{25}Cl_2N$: C, 70·6; H, 6·7; Cl, 18·9; N, 3·7; equiv. wt., 374. Found: C, 71·4; H, 6·5; Cl, 19·0; N, 3·9; equiv. wt., 372.

Acyloxy esters of acetylenic piperidinols. The following general method was used for the preparation of the esters. A mixture of the piperidinol, pyridine and acid anhydride was refluxed for 3 h, at the end of which time the solvent was evaporated under reduced pressure. The residue was converted to the hydrohalide. The esters prepared are shown in Table II.

Reduction of Acetylenic Piperidinols

(*a*) N-*Phenethyl-4-phenylethynyl-4-piperidinol.* (1) *Reduction with lithium aluminium hydride.* A solution of *N*-phenethyl-4-phenylethynyl-4-piperidinol (3·5 g) in tetrahydrofuran (50 ml) was added dropwise over a period of 0·5 h to a suspension of lithium aluminium hydride (0·4 g) in tetrahydrofuran (77 ml) and the mixture refluxed for 3 h. On cooling, the product was decomposed with damp tetrahydrofuran, filtered, and the solvent evaporated. The residual solid (3·35 g) crystallized from benzene to give *trans-N*-phenethyl-4-styryl-4-piperidinol (Isomer A), m.p. 127·5°.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82·0; H, 8·2; N, 4·6; equiv. wt., 307. Found: C, 82·3; H, 8·1; N, 4·7; equiv. wt., 307.

Ultraviolet absorption: λ_{max} 251 mμ, ε 21,193.

(2) *Reduction with* $Pd/CaCO_3$ *in ether.* Palladized calcium carbonate (5 per cent, 0·4 g) was added to a solution of *N*-phenethyl-4-phenylethynyl-4-piperidinol (8·66 g) in ether (200 ml) and the mixture shaken with hydrogen at room temperature and pressure. After 5 h the mixture was filtered and the filtrate evaporated to give a crystalline solid. Fractional crystallization

of this solid from benzene–petroleum ether (60–80°) gave the following fractions:

(i) unchanged *N*-phenethyl-4-phenylethynyl-4-piperidinol (3·0 g), m.p. and mixed m.p. 151·5°;

(ii) *N*-phenethyl-4-phenethyl-4-piperidinol (3·2 g), m.p. and mixed m.p. 95·5°;

(iii) *cis*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer B) (1·85 g), m.p. 60–62°.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82·0; H, 8·2; N, 4·6; equiv. wt., 307. Found: C, 81·6; H, 7·9; N, 4·8; equiv. wt., 310.

(3) *Reduction with* $Pd/CaCO_3$ *in ethanol.* The hydrogenation was repeated using *N*-phenethyl-4-phenylethynyl-4-piperidinol (4·3 g) and palladized calcium carbonate (5 per cent, 0·2 g), with ethanol (300 ml) as solvent, the mixture being shaken for 1·5 h. From the reaction mixture a solid (4·2 g) was obtained which crystallized from benzene–petroleum ether (40–60°) to give *N*-phenethyl-4-phenethyl-4-piperidinol, m.p. and mixed m.p. 95·5°. The hydrochloride from ethanol–ether had m.p. 183°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: C, 72·9; H, 8·2; N, 4·1; equiv. wt., 346. Found: C, 73·8; H, 8·3; N, 4·1; equiv. wt., 344.

(4) *Reduction with Lindlar catalyst.* A repeat experiment using *N*-phenethyl-4-phenylethynyl-4-piperidinol (5·0 g), ethanol (300 ml) and palladized calcium carbonate (5 per cent, 0·2 g) which had been previously poisoned with lead acetate was made. From the reaction product a yellow viscous oil (4·9 g) was obtained, which solidified on trituration with petroleum ether (40–60°). This solid on crystallization from benzene–petroleum ether (40–60°) gave *cis*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer B), m.p. and mixed m.p. 60°. The hydrochloride from ethanol–ether had m.p. 156·5°.

Anal. Calcd. for $C_{21}H_{26}ClNO$: C, 73·3, H, 7·6; N, 4·1; equiv. wt., 344. Found: C, 73·1, H, 7·5; N, 4·3; equiv. wt., 344.

Ultraviolet absorption: λ_{max} 245 mμ, ϵ 9,747.

(*b*) N-*Phenethyl-3-methyl-4-phenylethynyl-4-piperidinol.* A solution of *N*-phenethyl-3-methyl-4-phenylethynyl-4-piperidinol (5·8 g) in ethanol (300 ml) was hydrogenated in the presence of palladized charcoal (5 per cent, 0·3 g) to give *N*-phenethyl-3-methyl-4-phenethyl-4-piperidinol, m.p. 111–112° (from benzene–petroleum ether (40–60°)).

Anal. Calcd. for $C_{22}H_{29}NO$: C, 81·7; H, 9·1; N, 4·3; equiv. wt., 324. Found: C, 81·5; H, 8·9; N, 4·1; equiv. wt., 321.

(*c*) N-*Methyl-3-methyl-4-phenylethynyl-4-piperidinol.* A solution of N-methyl-3-methyl-4-phenylethynyl-4-piperidinol (Isomer A) (1·0 g) in ethanol (100 ml) hydrogenated in the presence of palladized charcoal (5 per cent, 0·1 g) gave an oil which on treatment with hydriodic acid gave *N*-methyl-3-methyl-4-phenethyl-4-piperidinol hydriodide (Isomer A), m.p. 159·5° (from ethanol–ether).

Anal. Calcd. for $C_{15}H_{24}INO$: C, 49·9; H, 6·7; N, 3·9; equiv. wt., 361. Found: C, 50·2; H, 6·7; N, 3·7; equiv. wt., 364.

N-Methyl-3-methyl-4-phenylethynyl-4-piperidinol (Isomer B) (1·0 g) treated in a similar manner gave *N*-methyl-3-methyl-4-phenethyl-4-piperidinol hydriodide (Isomer B), m.p. 130·5° (1·46 g).

Anal. Found: C, 50·2; H, 6·5; N, 3·7; equiv. wt., 362.

Acyloxy esters of the 4-styryl and 4-phenethyl-4-piperidinols. Two methods were used to prepare these esters: *Method A*, the pyridine method (previously described), and *Method B*, the lithium salt method.[19]

Method A. *N*-Phenethyl-4-phenethyl-4-piperidinol (2·0 g) gave *N*-phenethyl-4-acetoxy-4-phenethylpiperidine hydrochloride, m.p. 241° (2·1 g) (from ethanol).

Anal. Calcd. for $C_{23}H_{30}ClNO_2$: C, 71·2; H, 7·8; N, 3·6; equiv. wt., 388. Found: C, 71·5; H, 7·6; N, 3·9; equiv. wt., 387.

When an attempt was made to esterify *trans*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer A) (1·5 g) using the pyridine method, *N*-phenethyl-4-styryl-1,2,5,6-tetrahydropyridine hydrochloride, m.p. 252–254° (d.) (1·4 g) (from ethanol–ether), was obtained.

Anal. Calcd. for $C_{21}H_{24}ClN$: C, 77·4; H, 7·4; N, 4·3; equiv. wt., 326. Found: C, 77·6; H, 7·6; N, 4·2; equiv. wt., 327.

Ultraviolet absorption: λ_{max} 225·5 mμ, ϵ 14,000.

The B Isomer treated in a similar manner also gave *N*-phenethyl-4-styryl-12,5,6-tetrahydropyridine hydrochloride, m.p. and mixed melting point 252–254° (d.).

Method B. A solution of *trans*-*N*-phenethyl-4-styryl-4-piperidinol (Isomer A) (3·0 g) in ether (40 ml) was added dropwise to a stirred ethereal solution of phenyllithium prepared from bromobenzene (2·16 g) and lithium (0·18 g). The reaction mixture was refluxed for 0·25 h, and after cooling acetic anhydride (1·1 ml)

in ether (15 ml) was added dropwise, the stirring being continued for 3 h.

After decomposition with crushed ice and acetic acid (4·0 ml), the precipitate which formed was collected, dried and suspended in ether, and the suspension was made alkaline with ammonium hydroxide solution. The free base was extracted with ether and the solvent removed to give a yellow oil which on treatment with ethanolic hydrochloric acid gave a solid (3·2 g). This crystallized from ethanol–ether to give *trans*-*N*-phenethyl-4-acetoxy-4-styrylpiperidine hydrochloride (Isomer A), m.p. 247·5–249·5° (d.).

Anal. Calcd. for $C_{23}H_{28}ClNO_2$: C, 71·6; H, 7·3; N, 3·6; equiv. wt., 386. Found: C, 72·2, H, 7·5; N, 3·5; equiv. wt., 383.

Ultraviolet absorption: λ_{max} 252 mμ, ε 20,860.

cis-*N*-Phenethyl-4-styryl-4-piperidinol (Isomer B) (3·0 g) treated in a similar manner gave *cis*-*N*-phenethyl-4-acetoxy-4-styrylpiperidine hydrochloride (Isomer B), m.p. 190·5–191·5°.

Anal. Found: C, 71·8; H, 7·0; N, 3·4; equiv. wt., 388.

Ultraviolet absorption: λ_{max} 238 mμ, ε 8,782.

Reaction of phenethylmagnesium bromide with N-*phenethyl-3-methyl-4-piperidone.* An ethereal solution of *N*-phenethyl-3-methyl-4-piperidone (10·0 g) was added to a stirred solution of phenethylmagnesium bromide in ether (200 ml), prepared from phenethyl bromide (16·5 g) and magnesium (2·45 g), and the mixture was refluxed for 3 h. The product was decomposed with crushed ice and dilute hydrochloric acid, and the aqueous layer was separated, washed with ether and made alkaline with concentrated ammonium hydroxide solution. The base was extracted with ether (3 × 100 ml), and the combined ethereal extracts were washed with water (2 × 20 ml), dried, and evaporated under reduced pressure to give a viscous oil (8·4 g). This oil on trituration with petroleum ether (40–60°) solidified and on crystallization from benzene gave *N*-phenethyl-3-methyl-4-phenethyl-4-piperidinol, m.p. and mixed m.p. 111–112° (1·38 g). The mother liquors on evaporation gave an oil (6·7 g) from which a picrate, m.p. 169–170° (d.), was obtained. The m.p. was undepressed on admixture with an authentic sample of *N*-phenethyl-3-methyl-4-piperidone picrate, m.p. 169·5–170·5°.[1]

N-*Phenethyl-4-bromoethynyl-4-piperidinol hydrochloride.* This was prepared by a method analogous to that of Di Paco and

Tauro.[15] *N*-Phenethyl-4-ethynyl-4-piperidinol (10·0 g) was added in small portions with vigorous shaking to a cooled (0°) solution of sodium hypobromite prepared from bromine (7·0 g), sodium hydroxide (17·5 g) and water (70 ml). When the addition was complete the product was shaken for 1 h and then extracted with chloroform (3 × 100 ml). The combined chloroform extracts were dried and evaporated, and the residue was treated with ethanolic hydrochloric acid to give *N*-phenethyl-4-bromoethynyl-4-piperidinol hydrochloride, m.p. 192·5–195·5° (d.) (13·82 g) from ethanol–ether.

Anal. Calcd. for $C_{15}H_{19}BrClNO$: C, 52·3; H, 5·6; N, 4·1; equiv. wt., 345. Found: C, 52·6; H, 5·9; N, 4·1; equiv. wt., 343.

N-*Phenethyl-4-cyano-4-piperidinol.* A saturated aqueous solution of sodium cyanide (5·5 g) was added dropwise during a period of 1 h to a stirred cooled solution of *N*-phenethyl-4-piperidone (13·5 g) in dilute hydrochloric acid (15 per cent, 28·5 ml). After 2 h stirring, the precipitated material was filtered off and crystallized from benzene–petroleum ether (40–60°) to give *N*-phenethyl-4-cyano-4-piperidinol, m.p. 93° (12·3 g).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73·0; H, 7·9; N, 12·2; equiv. wt., 230. Found: C, 73·3; H, 7·9; N, 12·2; equiv. wt., 223.

N-Phenethyl-4-cyano-4-piperidinol (2·0 g) when esterified by the pyridine method gave *N*-phenethyl-4-acetoxy-4-cyanopiperidine hydrochloride, m.p. 258·5° (1·82 g).

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2$: C, 62·2; H, 6·9; Cl, 11·5; N, 9·1; equiv. wt., 309. Found: C, 62·1; H, 6·8; Cl, 11·5; N, 9·0; equiv. wt., 306.

N-*Phenethyl-4-cyano-4-propionoxypiperidine hydrochloride*, m.p. 245° (1·78 g) (from ethanol–ether) was prepared from *N*-phenethyl-4-cyano-4-piperidinol (2·0 g), propionic anhydride (3·0 ml) and pyridine (3·0 ml).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_2$: C, 63·2; H, 7·2; Cl, 11·0; N, 8·7; equiv. wt., 323. Found: C, 62·9; H, 7·3; Cl, 10·8; N, 8·7; equiv. wt., 322.

N-*Phenethyl-4-carboxy-4-piperidinol.* A mixture of *N*-phenethyl-4-cyano-4-piperidinol (10·0 g) and concentrated hydrochloric acid (20 ml) was heated on a steam bath for 20 h. On cooling, the solution was made alkaline with ammonium hydroxide solution and extracted with ether (3 × 50 ml), and the combined ethereal

extracts were dried (anhyd. Na_2SO_4). On evaporation an oil (3·4 g) was obtained, and this on treatment with ethanol hydrochloric acid gave *N*-phenethyl-4-carboxy-4-piperidinol hydrochloride, m.p. 176·5° (2·8 g) from ethanol–ether.

Anal. Calcd. for $C_{14}H_{20}ClNO_3$: C, 58·8; H, 7·1; Cl, 12·4; N, 4·9; equiv. wt., 286. Found: C, 58·9; H, 7·4; Cl, 12·4; N, 5·1; equiv. wt., 284.

Equivalent weights of the bases were determined by titration with 0·2N perchloric acid in acetic acid with Oracet Blue as indicator. Titrations of salts were carried out in the same solvent in the presence of mercuric acetate, by the method of Pifer and Wollish.[32]

Summary. Some *N*-substituted-4-acetylenic-4-piperidinols and their acyloxy esters have been synthesized and assessed as potential analgesics to evaluate the effect of replacing the 4-phenyl group in analgesics of the prodine type by an ethynyl or substituted ethynyl group. *N*-Phenethyl-4-phenylethynyl-4-piperidinol has been reduced to the 4-styryl and 4-phenethyl analogues. The compounds have been assessed for 'analgesic activity' by the hot-plate method and some by a tail-pinch method. Although a number of the compounds possess central nervous system activity it appears improbable that they were true morphine-like analgesics.

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