1340; $[\alpha]_D$ + 28°); 3-cyclopentoxy-11β-nitro-1,3,5(10)-estratrien-9α-ol-17-one (X; mp 218–223 °C; λ_{max} 277 nm; ε = 1540; $[\alpha]_D$ + 27°); 3-methoxy-11β-nitro-1,3,5(10)-estratrien-9α-ol-17-one (XI; mp 218–221 °C; λ_{max} 277.5, 285 nm; ε = 1860, 1640; $[\alpha]_D$ + 32°); 3-methoxy-17α-ethynyl-11β-nitro-1,3,5(10)-estratriene-9α,17β-diol (XII; amorphous; λ_{max} 277.5, 285 nm; ε = 2480, 2200; $[\alpha]_D$ −83°); 3-methoxy-11β-nitro-1,3,5(10)-estratriene-9α,17β-diol 17-acetate (XIII; mp 180–182 °C; λ_{max} 277, 284 nm; ε = 2030, 1770; $[\alpha]_D$ − 49°); 3-methoxy-11β-nitro-1,3,5(10)-estratriene-9α,17β-diol 17-cyclopentylpropionate (XIV; mp 145–146 °C; λ_{max} 277.5, 285 nm; ε = 1650, 1470; $[\alpha]_D$ − 28°).

Table II. Estrogenic activity of 9α-OH, 11β-NO_2-steroids

Compound	Minimal effective dose (μg)		
	s.c.	os	os/s.c.
Estrone	3	100	33
Estradiol	0.3	30	100
Ethinylestradiol	0.3	3	10
II	3	3	1
IV	3	1	0.3
V	30	30	1
VII	3	3	1
VIII	3	3	1
IX	3	3	1
X	1	1	1
XI	3	3	1
XII	1	1	1
XIII	3	1	0.3
XIV	3	3	1

The compounds listed in Table I were assayed for estrogenic activity in castrated female rats either by s.c. or by oral route. The estrogenic effect was determined by the modifications of the vaginal cytology changing from the diestrous pattern (negative smear) to the proestrus-estrus type (positive smear). The minimum effective dose (MED) was considered as the one producing a positive smear in 1 out of 3 rats or in 2 out of 5.

As shown in Table II, all the compounds of the series display a high estrogenic activity and show MED of the same order by s.c. and by oral route (os) (ratio os/s.c. $\simeq$ 1). The reference compounds are, instead, much less active by oral than by s.c. administration, thus giving higher os/s.c. ratios.

In conclusion, the 9α-OH, 11β-NO_2-steroids are potent estrogenic agents by oral route, despite the fact that they do not possess the 17α-ethynyl group which is generally introduced into a steroidal molecule in order to achieve oral activity.

The absence of the 17α-alkyl group seems to be interesting in view of a possible clinical application, since 17α-alkyl steroids are generally considered to impair the liver function.

Riassunto. Per azione dell'acido nitrico su 1,3,5(10),9(11)-estratetraeni sono stati ottenuti 9α-idrossi-11β-nitro-1,3,5(10)-estratrieni, i quali hanno mostrato una interessante attività estrogena sia per via orale che per via sottocutanea.

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Anaesthetic Properties of Some Esters of 2-Piperidylcarbinols

Anaesthetic activity was unexpectedly found among some diphenylacetyl esters of 2-piperidylcarbinols synthetized for pharmacological screening: subsequent work on these new and related compounds, reported in the Table shed some light on the structure-activity relationship and the conclusions are briefly reported here.

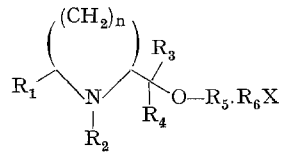
Chemistry. The amino alcohols employed in the synthesis of the compounds reported in the Table were obtained according to one of the following procedures: (a) Condensation between pyridine and acetone[1], cyclopentanone[2] or cyclohexanone[2] in the presence of Mg/$HgCl_2$ afforded the 2-pyridylcarbinols which were reduced (PtO_2 in EtOH) to give the corresponding 2-piperidylcarbinols. Equimolar amounts of a 2-piperidylcarbinol and an aldehyde (mostly formaldehyde) were hydrogenated at 30 atm in EtOH with Pd/C catalyst to yield the N-alkyl-2-piperidylcarbinols used in the preparation of compounds 1,4÷11. (b) The methyl ester of D or L 1-methylpipecolic acid[3], *cis* or *trans* 1,6-dimethylpipecolic acid[4] or 1-methylproline[5] was added to a large excess of an ethereal solution of CH_3MgBr. In these conditions, inversion at C_2 was minimized and in this way the aminoalcohols employed for the preparation of compounds 2, 3, 14, 15, 16 were obtained. (c) 1-methyl-2-piperidylcarbinol[6] and 1α-dimethylpiperidylcarbinol[7] (unknown isomer) used in the synthesis of compounds 13 and 12, were prepared according to the literature.

The aminoalcohols were esterified in pyridine with the appropriate acyl chloride to give the esters reported, with the exception of compound 7 which was obtained by reduction of the nitrobenzoyl ester and compound 9 which was obtained by brief hydrolysis of the diphenylchloroacetyl ester as reported by King and Holmes[8].

Pharmacology. Local anaesthetic activities of the compounds reported in the Table have been evaluated according to the Chance-Lobstein[9] test (corneal anaesthesia). Each substance was tested at varying concentrations by the administration of 0.1 ml of a 0.85% saline solution under the eyelids of guinea-pigs.

[1] B. Emmert and E. Asendorf, Chem. Ber. *72*, 1188 (1939).
[2] B. Emmert and E. Pirot, Chem. Ber. *74*, 714 (1941).
[3] R. Lukas, J. Kloubek, K. Blaha and J. Kovar, Colln Czech. chem. Commun. *22*, 286 (1957).
[4] W. Barbieri, L. Bernardi and P. Maggioni, to be published (1969).
[5] P. Karrer and R. Widmer, Helv. chim. Acta *8*, 364 (1925).
[6] F. F. Blike and Chi-Jung Lu, J. Am. chem. Soc. *77*, 29 (1955).
[7] R. G. Cleino, R. Raper and H. J. Vipond, J. chem. Soc. 2095 (1942).
[8] F. E. King and D. Holmes, J. chem. Soc. 164 (1947).
[9] M. R. A. Chance and H. Lobstein, J. Pharmac. exp. Ther. *82*, 203 (1944).

The eyes were kept open for 30 sec and after a further 60 sec the corneal reflex was tested by touching the centre of the cornea with a horsehair capable of exercising a force of 200 mg before flexing. The stimulation was effected once every minute for 5 min, the procedure then being repeated on the other eye. Each concentration was tested on 10 animals giving a total of 100 responses. The median anaesthetic concentrations (EC_{50}) reported in the Table have been calculated according to the method of FINNEY[10] on the basis of the percentage of positive responses (i.e. the absence of corneal reflex).



No.[a]	Form	n	R_1	R_2	R_3	R_4	R_5	R_6	X	mp	Corneal anaesthesia[e] EC_{50} (mg/ml)
1	DL	3	H	CH_3	CH_3	CH_3	Diphenylacetyl	H	Cl	168°	0.85
2[b]	D	3	H	CH_3	CH_3	CH_3	Diphenylacetyl	H	Cl	164°	0.66
3[c]	L	3	H	CH_3	CH_3	CH_3	Diphenylacetyl	H	Cl	164°	1.1
4	DL	3	H	CH_3	CH_3	CH_3	Diphenylacetyl	CH_3	I	172°	i.a.
5	DL	3	H	$CH_3CH_2C_6H_5$	CH_3	CH_3	Diphenylacetyl	H	Cl	166°	i.a.
6	DL	3	H	CH_3	CH_3	CH_3	Phenylacetyl	H	Cl	135°	6.4
7	DL	3	H	CH_3	CH_3	CH_3	*p*-aminobenzoyl	–	–	159°	i.a.
8[d]	DL	3	H	CH_3	CH_3	CH_3	Phenylcyclopentyl-acetyl	H	Cl	–	4.9
9	DL	3	H	CH_3	CH_3	CH_3	Diphenylglycolyl	H	Cl	166°	1.0
10	DL	3	H	CH_3	$-(CH_2)_4-$		Diphenylacetyl	H	Cl	165°	10.0
11	DL	3	H	CH_3	$-(CH_2)_5-$		Diphenylacetyl	H	Cl	164°	i.a.
12	DL	3	H	CH_3	CH_3	H	Diphenylacetyl	H	Cl	193°	1.9
13	DL	3	H	CH_3	H	H	Diphenylacetyl	H	Cl	200°	1.7
14[f]	L	2	H	CH_3	CH_3	CH_3	Diphenylacetyl	$C_4H_6O_6$		135°	i.a.
15	DL *cis*	3	CH_3	CH_3	CH_3	CH_3	Diphenylacetyl	H	Cl	197°	1.25
16	DL *trans*	3	CH_3	CH_3	CH_3	CH_3	Diphenylacetyl	H	Cl	175°	1.85
Procaine, HCl											48.6
Lidocaine, HCl											23.0

[a] All the compounds gave satisfactory elemental analysis (C, H, N). [b] $[\alpha]_D^{20} + 10.5$ ($c = 1$, H_2O). [c] $[\alpha]_D^{20} - 11$ ($c = 1$, H_2O). [d] Amorphous. [e] i.a., inactive at the maximum permissible concentration. [f] Tartrate. $[\alpha]_D^{20} + 23$ ($c = 1$, EtOH).

Structure-activity relationship. From the data in the Table the following observations can be made: (a) Good anaesthetic activity has been found only in compounds having 2 phenyl groups in the acyl residue (cf. 1 and 9 with 6, 7 and 8): particular mention should be made of the fact that the *p*-aminobenzoate (No. 7) is practically inactive. (b) On quaternization (No. 4) the activity is lost. (c) Optimum activity has been found for $R_3 = R_4 = CH_3$ (Nos. 1, 9, 15 and 16); when R_3 and R_4 form part of a cyclic structure (Nos. 10 and 11) the activity is strongly reduced. (d) The anaesthetic activity seems to be strongly dependent on the size of the ring (Nos. 3 and 14), but is relatively independent of subtle steric effects as shown by the fact that there is only a limited difference in activity between D and L forms (Nos. 2 and 3) and between the *cis* and *trans* forms of the 6-methyl derivatives (Nos. 15 and 16).

Riassunto. Vengono brevemente discussi i rapporti fra struttura e attività anestetica di un gruppo di difenilacetati di amino alcoli ciclici riportati nella tabella

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[10] D. J. FINNEY, *Probit Analysis* (Cambridge University Press, London 1947).

A New Guanidine Alkaloid[1]

The crude mixture of alkaloids obtained from the alcoholic extract of the bark of *Pterogyne nitens* Tul. (Leguminosae) was subjected to column chromatography on alumina followed by purification through the picrate.

A new alkaloid named pterogynine (I) was isolated as the picrate salt (mp 157–158 °C) and further characterized as perchlorate (mp 101–102 °C) and hydrochloride (mp 142–143 °C). There were difficulties in determining the molecular formula because of the explosive decomposition of the salts during some of the combustion analyses. The analytical data of the 3 salts and proton-counting in the NMR-spectrum (in $CDCl_3$) of the hydrochloride led to the probable molecular composition $C_{11}H_{21}N_3$ for the free base. This was ascertained by the mass spectrum of the

[1] Part XIV of *Studies on Plants*; preceding part, R. A. CORRAL, O. O. ORAZI and I. A. BENAGES, Tetrahedron Letters *545* (1968).