RESEARCH PAPERS

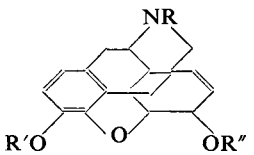
MORPHINE DERIVATIVES WITH ANTIANALGESIC ACTION

By A. F. Green, G. K. Ruffell and E. Walton

From the Wellcome Research Laboratories, Beckenham.

Received January 5, 1954

The first morphine derivatives found to antagonise the actions of morphine were *N*-allylnorcodeine (I; R = $CH_2 \cdot CH : CH_2$, R′ = CH_3, R″ = H) and *N*-allyldihydronorcodeine (Pohl[1], von Braun[2]). Several other unsaturated *N*-alkyl derivatives of norcodeine were later examined, and some were found to have a similar but weaker action[3].



(I)

In view of this activity, it is surprising that no corresponding derivative of normorphine was made until 1941–42, when *N*-allylnormorphine (nalorphine) (I; R = C_3H_5, R′ = R″ = H) was prepared[4,5] and found to have a much higher antianalgesic activity than that of *N*-allylnorcodeine[6,7].

As no other *N*-derivatives of normorphine had at the time been described, we prepared and examined a series of such derivatives (Table I) and found that antianalgesic activity was conferred by saturated as well as unsaturated *N*-alkyl groups. The activity of *N*-propylnormorphine (I; R = C_3H_7, R′ = R″ = H), for example, is equal to that of the *N*-allyl analogue (I; R = C_3H_5, R′ = R″ = H). A similar but more extensive series has recently been described by Clark, Pessolano, Weijlard and Pfister 3rd[8] with comparable results.

Our compounds were all obtained by direct alkylation of normorphine in alkaline ethanolic solution. In addition to these, *N*-derivatives, *N*:*O*-diethyl- and *N*:*O*-dipropylnormorphine (I; R = R′ = C_2H_5, R″ = H; and R = R′ = C_3H_7, R″ = H) were also obtained on introduction of the ethyl and propyl group respectively, but alkylation with *iso*-propyl halide gave only *O*-*iso*propylnormorphine (cf. Clark *et al.*, loc. cit.). *O*-derivatives were not isolated when the unsaturated residues, allyl, crotyl and propargyl, were introduced.

A useful method of distinguishing the various types of derivatives obtained was provided by their reaction with nitrous acid, as described in the Experimental Section.

PHARMACOLOGY

Methods.

Analgesic action was determined in 3 to 4 week old rats of an inbred Wistar strain. Their pain thresholds were measured 30 minutes after subcutaneous injection of the compounds by the heat and pressure methods described by Green and Young[9]. Every compound was tested at a dose of 50 mg./kg. and the active ones at lower doses. Analgesic ED50 values were determined from the relationship of log. dose to the probit of the number of animals in the group whose pain thresholds were at least twice the mean of controls, in tests where each of 3 doses related as 1 : 2 : 4 were injected in groups of ten rats. Analysis of several such tests of morphine showed that the ED50 was not constant from day to day, with a standard deviation of the log ED50 of 0·165 for heat (13 degrees of freedom) and 0·100 for pressure (19 d.f.).

Antianalgesic action was determined in a similar manner. The compounds were injected subcutaneously at the same time as, but at different sites from 10 mg./kg. of morphine sulphate. This dose of morphine is about 4 times its ED50 and at least twice the amount usually necessary to double the pain threshold in all rats. The analgesic action of this amount of morphine could be almost completely eliminated by *N*-allylnormorphine or by other effective antagonists. We have estimated the doses of the compounds required to reduce the incidence of a doubling of pain-threshold to 50 per cent., by probit analysis of tests in which 3 doses related as 1 : 4 : 16 were each injected into groups of ten rats. These doses are referred to as the antianalgesic ED50's. The dose-response lines are considerably less steep (b, usually between 1·5 and 3·0) in these tests than in the analgesic tests (b, usually between 2·5 and 5·0), and the limits of error of the antianalgesic ED50 of a compound are correspondingly greater. Analysis of the tests summarised in Table I showed the standard deviation of the log ED50 of a compound in antianalgesic tests on different occasions to be of the order of 0·30 for heat (16 d.f.) and 0·18 for pressure (12 d.f.).

Results.

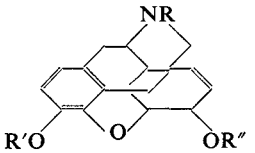
Comparison of the ED50 values (Table I) shows that the length of the *N*-alkyl substituent (R) has an important influence on pharmacological action in *N*-alkyl substituted derivatives of morphine. Analgesic activity is quite the greatest when the substituent is methyl, as in morphine, and its diacetyl and dipropionyl derivatives. (The latter has been examined previously only by von Mering[10].) The ethyl compound ($R = C_2H_5$, $R' = R'' = H$) has a moderate action, whereas the compounds with propyl, allyl and larger substituents have scarcely any analgesic effect. The greatest antagonistic action was shown by the propyl and allyl substituted compounds, and a lower activity was found in the butyl, crotyl and ethyl derivatives. The gradation of analgesic and antianalgesic activity with variation of the *N*-alkyl substituent, and the finding that the

ethyl and propargyl compounds show both effects to some extent, support the contention that morphine antagonists, such as nalorphine, act by competition for the same receptors as does morphine.

The influence of various R′ and R″ substituents of *N*-allylnormorphine on antianalgesic activity to some extent parallels that of the same sub-

TABLE I

ANALGESIC AND ANTIANALGESIC ACTION OF THE MORPHINE DERIVATIVES



ED50 values are given in terms of base

R	R′	R″	ED50 mg./kg. or the effect of 50 mg./kg.			
			Analgesia		Antianalgesia (morphine sulphate, 10 mg./kg.)	
			Heat	Pressure	Heat	Pressure
Morphine types						
H (normorphine)	H	H	not tested	slight	not tested	slight
CH_3 (morphine)	H	H	2·0 (14)	1·6 (20)	none	none
$CH_3{\cdot}CH_3$	H	H	moderate	moderate	slight	slight
$CH_2{\cdot}CH_2{\cdot}CH_3$	H	H	none	none	0·71 (3)	0·75 (3)
$CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	H	H	none	none	7·9 (2)	9·0 (2)
$CH_2{\cdot}CH{:}CH_2$ (*N*-allylnormorphine)	H	H	none	none	0·41 (11)	0·79 (5)
$CH_2{\cdot}CH{:}CH{\cdot}CH_3$	H	H	none	none	3·9 (2)	5·9 (2)
$CH_2{\cdot}C{:}CH$	H	H	moderate at 20 to 50 mg./kg.	moderate at 20 to 50 mg./kg.	13 (1)	20 (1)
Codeine types						
H	CH_3	H	slight	slight	none	none
CH_3 (codeine)	CH_3	H	5·5 (2)	7·5 (2)	none	none
$CH_3{\cdot}CH_2{\cdot}CH_3$	CH_3	H	none	none	6 (1)	4·2 (2)
$CH_2{\cdot}CH{:}CH_2$ (*N*-allylnorcodeine)	CH_3	H	none	slight	22 (2)	37 (2)
Acetyl and propionyl derivatives						
CH_3 (diamorphine)	$CO{\cdot}CH_3$	$CO{\cdot}CH_3$	0·3 (2)	0·3 (2)	none	none
CH_3	$CO{\cdot}C_2H_5$	$CO{\cdot}C_2H_5$	0·5 (2)	0·5 (2)	none	none
$CH_2{\cdot}CH{:}CH_2$	$CO{\cdot}CH_3$	$CO{\cdot}CH_3$	slight	moderate	0·86 (2)	2·7 (2)
$CH_2{\cdot}CH{:}CH_2$	$CO{\cdot}C_2H_5$	$CO{\cdot}C_2H_5$	*Ca.* 40	*Ca.* 40	1·4 (1)	2·3 (3)
Miscellaneous						
H	$CH(CH_3)_2$	H	slight	slight	none	none
$CH_2{\cdot}CH_3$	$CH_2{\cdot}CH_3$	H	slight	moderate	none	none
$CH_2{\cdot}CH_2{\cdot}CH_3$	$CH_2{\cdot}CH_2{\cdot}CH_3$	H	none	none	50 (1)	50 (1)

The figures in parentheses are the number of tests from which the mean ED 50's were derived.

stituents on the analgesic action of morphine. Just as methylation of the R′ hydroxyl group (as in codeine) reduced the analgesic action of morphine, so too does methylation reduce the activity of *N*-allyl and *N*-propylnormorphine. The diacetyl and dipropionyl derivatives of *N*-allylnormorphine are powerful antianalgesics just as the corresponding derivatives of morphine are powerful analgesics, but in contrast to the morphine derivatives they are not more active than the parent compound. In none of the compounds described here, nor in any of those investigated elsewhere, has any modification of the R′ and R″ substituents of morphine resulted in a manifestation of antianalgesic actions. It seems justifiable

therefore to conclude that both the nature of the action of morphine derivatives (I)—analgesic or antianalgesic—and the degree of activity are governed in some way by the properties conferred by the R′ substituent, whereas the R′ and R″ affect only the degree of activity.

The antianalgesic action of *N*-propylnormorphine and the diacetyl derivative of *N*-allylnormorphine have been examined in greater detail. Like *N*-allylnormorphine they antagonise not only the analgesic action of morphine, but also that of such pharmacologically similar but chemically different compounds as methadone, pethidine and thiambutene. They have reduced or eliminated the analgesic and respiratory actions of each of these compounds in rats and rabbits at doses similar to the effective doses of *N*-allylnormorphine. The *N*-propyl compound has also been found to eliminate morphine narcosis in dogs, and to inhibit the depressor action of morphine on temperature in the rabbit and on the stretch reflex of isolated guinea-pig ileum. A more detailed account of the properties of this compound will be published separately.

Experimental Chemistry

Dipropionylmorphine (I; R = CH_3, R′ = R″ = COC_2H_5), first described by Hesse[11] as amorphous, crystallised from dilute ethanol in rhombs, m.pt. 99° to 101° C. Found: N, 3·5; C_2H_5CO, 28·9. Calc. for $C_{23}H_{27}NO_5$: N, 3·5; C_2H_5CO, 28·7 per cent.

Preparation of normorphine (I; R = R′ = R″ = H). The following process is an improvement on the 2-stage hydrolysis of *N*-cyandiacetylnormorphine (I; R = CN, R′ = R″ = $COCH_3$) described by von Braun.[12] A mixture of *N*-cyandiacetylnormorphine (268 g.) and 1·66N hydrochloric acid (4020 ml.) was refluxed for 4 hours. After a further 15 hours at 20° C., the resulting solution was evaporated *in vacuo* to a smaller volume (1500 ml.) from which normorphine hydrochloride, m.pt. 315° to 318° C., separated. Further crops from the mother liquors brought the total yield up to 200 g. (90 per cent.).

N-*Carbamidonormorphine* (I; R = $CONH_2$, R′ = R″ = H)[13]. *N*-Cyandiacetylnormorphine (2 g.) heated under reflux with 1·66 N hydrochloric acid (30 ml.) for the minimum time required to obtain a clear solution (about 1 hour), was partially hydrolysed to N-*Carbamidonormorphine* 0·6 g.), which slowly separated on cooling. This amide crystallised from water, in which it is sparingly soluble, in slender prisms, decomposing at 265° to 285° C., depending on the rate of heating. Found: C, 65·2; H, 5·8; N, 8·7; O, 20·5. $C_{17}H_{19}N_2O_4$ requires C, 65·0; H, 5·7; N, 8·9; O, 20·4 per cent.

N-*Ethylnormorphine* (I; R = C_2H_5, R′ = R″ = H) *and* N:O-*Diethylnormorphine* (I; R = R′ = C_2H_5, R″ = H). A mixture of normorphine (8·5 g.), ethyl iodide (2·65 ml.), sodium hydroxide (1·3 g.) and methanol (60 ml.) was heated under reflux for 2¾ hours. The resulting solution was evaporated to dryness *in vacuo* and the residue dissolved in dilute hydrochloric acid. The acid solution, clarified with charcoal and adjusted to *p*H 8, yielded a gum, which was extracted with chloroform. This extract, on evaporation, gave a residue which was partially solidified

by rubbing with ether (A). The resulting solid, consisting of crude *N*-ethylnormorphine, was collected, and purified by dissolving in a hot ethanolic solution of anhydrous oxalic acid, when the acid *oxalate* separated as a granular precipitate which crystallised from aqueous ethanol in slender prisms, m.pt. 225° C. (decomp.). Found: C, 61·0; H, 5·9; N, 3·7. $C_{18}H_{21}NO_3,C_2H_2O_4$ requires C, 61·7; H, 5·9; N, 3·6 per cent. *N*-Ethylnormorphine, obtained by neutralising an aqueous solution of the oxalate, formed granular crystals, m.pt. 195° to 198° C. (Clark *et al.*[8] give m.pt. 217° to 218° C.). Found: N, 4·5; O, 15·9. Calc. for $C_{18}H_{21}NO_3$: N, 4·7; O, 16·1 per cent. The *hydrobromide* decomposed at 170° to 200° C. Found: Br, 21·2. $C_{18}H_{21}NO_3$, HBr requires Br, 21·1 per cent.

The ethereal extract (A), on evaporation, yielded a gum which, on rubbing with sodium hydroxide solution, slowly solidified to give crude N:O-*diethylnormorphine*. It crystallised from aqueous ethanol in tablets, m.pt. 83° to 85° C. Found: C, 69·3; H, 8·0; N, 4·2; O, 17·6; H_2O, 5·2; OEt, 13·3. $C_{20}H_{25}NO_3$, H_2O requires C, 69·6; H, 7·8; N, 4·1; O, 18·5; H_2O, 5·2; OEt, 13·1 per cent. (*cf. O*-Ethylnormorphine, m.pt. 156° C.[2]).

N-n-*propylnormorphine* (I; R = *n*-C_3H_7, R′ = R″ = H) *and* N:O-1-*Dipropylnormorphine* (I; R = R′ = *n*-C_3H_7, R″ = H). A solution of sodium hydroxide (0·8 g.) in methanol (12 ml.) was added over a period of 1 hour to a mixture of normorphine (5·42 g.), *n*-propyl iodide (1·95 ml.) and methanol (35 ml.) heated under reflux. After a further 9 hours' refluxing, the mixture was evaporated to dryness *in vacuo* and the residue stirred with chloroform. The insoluble solid consisting largely of sodium iodide was removed, repeatedly if necessary, and the clear filtrate evaporated to dryness. The residue was now dissolved in dilute hydrochloric acid. This solution was clarified by shaking with ether, adjusted to *p*H 8·8 and the base, which separated, again extracted with chloroform. Removal of the chloroform gave a residual base, which was taken up in ether. Concentration of this ether solution (B) gave a crystalline deposit of N-*propylnormorphine* (1·1 g.) which crystallised from ethanol in irregular leaflets, m.pt. 225° to 228° C. Found: C, 72·8; H, 7·2; N, 4·4; O, 14·7. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·3; N, 4·5; O, 15·3 per cent. The *hydrobromide* crystallised from water in pentagonal leaflets, decomposing at 195° to 215° C. Found: N, 3·4; Br, 19·8. $C_{19}H_{23}NO_3$, HBr requires N, 3·4; Br, 20·3 per cent. The *acid oxalate* separated from ethanol in leaflets, m.pt. 248° to 251° C. (decomp.). Found: N, 3·7; O, 25·5. $C_{19}H_{23}NO_3$, $C_2H_2O_4$ requires N, 3·5; O, 27·8 per cent.

The filtrate from solution (B), after extraction with dilute sodium hydroxide solution and evaporation, gave an oil consisting largely of N:O-*dipropylnormorphine* (1·5 g.), the *hydrobromide* of which crystallised from water in hexagonal plates, m.pt. 118° to 122° C., or from ethanol-ether in needles, with a less definite m.pt. Found: C, 57·7; H, 7·1; O, 13·8; N, 3·1; Br, 18·0; C_3H_7O, 13·8. $C_{22}H_{29}NO_3$, HBr, H_2O requires C, 58·1; H, 7·1; O, 14·1; N, 3·1; Br, 17·6; OC_3H_7 14·1 per cent.

N-Propylnorcodeine (I; R = C_3H_7, R′ = CH_3, R″ = H) could not be

obtained as a crystalline hydrochloride[2], but its *hydrobromide* separated from wet acetone in needles, m.pt. 193° to 200° C. Found: N, 3·4; Br, 18·8; H_2O, 4·6. $C_{20}H_{25}NO_3$, HBr, H_2O required N, 3·3; Br, 18·8; H_2O, 4·2 per cent.

O-iso*Propylnormorphine* (I; R = R′ = H, R″ = $CH(CH_3)_2$). Normorphine (5·4 g.), *iso*propyl iodide (2 ml.), and sodium hydroxide (0·8 g.) in methanol (50 ml.) were heated under reflux for 8 hours. The solvent was removed and the residue extracted with chloroform. This extract, after being washed with dilute sodium hydroxide solution, gave on evaporation a gum, which solidified on rubbing with ether. The resulting solid (2 g.) consisting of O-iso*propylnormorphine*, was crystallised from benzene-light petroleum (b.pt. 60° to 80° C.) in rectangular tablets, m.pt. 139° to 141° C. Found: C, 72·6; H, 7·5; O, 15·0; N, 4·7. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·3; O, 15·3; N, 4·5 per cent.

The N-*nitroso* derivative crystallised from ethanol in triangular leaflets, m.pt. 165° C. Found: N, 8·1. $C_{19}H_{22}N_2O_4$ requires N, 8·2 per cent.

N-n-*Butylnormorphine* (I; R = *n*-C_4H_9, R′ = R″ = H). Normorphine (5·42 g.) was treated with *n*-butyl iodide (2·3 ml.) as described in the previous experiment. The methanol was removed and the residue dissolved in dilute hydrochloric acid. After being well washed with ether, the yellow hydrochloride solution was taken to about *p*H 10, the sticky precipitate extracted with ether, and the latter concentrated to a syrup, which on scratching partly solidified. Filtration gave an oil, probably containing *O*-butyl derivatives (not isolated), and solid *N-n*-butylnormorphine (0·5 g.) which crystallised best from ether in minute granules, m.pt. 193° to 195° C. (Clark *et al.*[8] give m.pt. 200 to 202° C.). Found: C, 73·5; H, 7·9; O, 14·7; N, 4·5. Calc. for $C_{20}H_{25}NO_3$: C, 73·4; H, 7·7; O, 14·7; N, 4·3 per cent.

N-*Allylnormorphine* (I; R = C_3H_5; R′ = R″ = H). Normorphine (140 g.), allyl bromide (45 ml.) and sodium hydroxide (20·7 g.) in methanol (300 ml.) were allowed to reflux for 3 hours, and the product evaporated to dryness. The residue, adjusted to *p*H 8·5, was well shaken with chloroform, and the two layers filtered from undissolved solid. The chloroform layer from the filtrate was evaporated, and the residue treated with ether. The resulting solid, consisting of crude *N*-allylnormorphine (98 g.) was purified by conversion to its hydrobromide, which crystallised from water as a dihydrate in well-defined needles, m.pt. 109° C. Found: H_2O, 8·7. $C_{19}H_{21}NO_3$, HBr, $2H_2O$ requires H_2O, 8·4 per cent.

N-*Allyl*-O : O-*diacetylnormorphine* (I; R = C_3H_5, R′ = R″ = $COCH_3$), from *N*-allylnormorphine and acetic anhydride, crystallised from ethanol in rhombs, m.pt. 134° to 135° C. Found: N, 3·6; $COCH_3$, 21·0. $C_{23}H_{25}NO_5$ requires N, 3·5; $COCH_3$, 21·8 per cent. Its *hydrochloride* crystallised from ethanol in needles, m.pt. 227° to 229° C. Found: Cl, 8·5. $C_{23}H_{25}NO_5$, HCl requires Cl, 8·2 per cent.

N-*Allyl*-O : O-*dipropionylnormorphine* (I; R = C_3H_5, R′ = R″ = COC_2H_5), prepared in a similar way using propionic anhydride, crystallised from ethanol in rectangular prisms, m.pt. 120° to 123° C. Found: N, 3·1; COC_2H_5, 27·4. $C_{25}H_{29}NO_5$ requires N, 3·3; COC_2H_5, 27·0 per

cent. Its *hydrochloride* crystallised from the same solvent in leaflets, m.pt. 220° to 224° C. Found: Cl, 7·4. $C_{25}H_{29}NO_5$, HCl requires Cl, 7·7 per cent.

N-*Crotylnormorphine* (I; R = CH_2·CH:CH·CH_3; R′ = R″ = H). Molecular proportions of normorphine, crotyl bromide and sodium hydroxide were allowed to react in methanol, as described above. The product was acidified with hydrochloric acid and evaporated, the residue redissolved in water, and the filtrate treated with sodium carbonate. The base was extracted with chloroform and subsequently taken up in ether. The ethereal solution was quickly extracted with 0·1N sodium hydroxide, which was then immediately neutralised to give crude *N*-crotylnormorphine base (1·6 g. from 6 g. of normorphine). Its *hydrobromide* crystallised from water in needles, m.pt. 100° to 118° C. (frothing). Found: C, 53·8; H, 6·4; O, 18·4; Br, 18·1; H_2O, 8·5. $C_{20}H_{23}NO_3$, HBr, $2H_2O$ requires C, 54·3; H, 6·3; O, 18·1; Br, 18·1; H_2O, 8·1 per cent.

N-*Propargylnormorphine* (I; R = CH_2·C:CH; R′ = R″ = H) was prepared by means of propargyl bromide, the crude base being extracted with chloroform as described above for the *N*-crotyl derivative. The chloroform residue was further purified by extracting with benzene. Evaporation of the benzene solution and treatment of the residue with a little ether gave N-*propargylnormorphine*, the *hydrobromide* of which, after washing with hot ethanol to remove colour, crystallised from methanol-ether in granules, m.pt. 243° to 245° C. Found: C, 58·5; H, 5·62; Br, 20·5. $C_{19}H_{19}NO_3$, HBr requires C, 58·5; H, 5·1; Br, 20·5 per cent.

Reaction of Morphine Derivatives with Nitrous Acid. The derivative (I) (10 mg.) was dissolved in 0·4N hydrochloric acid (1 ml.), treated with 10 per cent. sodium nitrite (0·4 ml.) and the mixture warmed gently to about 30° C. Normorphine (R = R′ = R″ = H) gave a yellow precipitate of the nitroso derivative (Speyer and Walther[14]); those with R = R′ = H, R″ = alkyl gave almost colourless derivatives, and those with R = saturated or unsaturated alkyl and R′ = R″ = H gave a yellow solution, while those with R^1 = saturated or unsaturated alkyl, R^2 = alkyl, and R″ = H, gave neither colour nor precipitate.

Summary

1. A series of *N*-alkyl substituted derivatives of morphine has been synthesised and examined for analgesic and antianalgesic action.

2. Several of these compounds have shown powerful antianalgesic activity, *N*-propylnormorphine and the diacetyl and dipropionyl derivatives of *N*-allylnormorphine (nalorphine) being about as active as nalorphine.

The authors are indebted to Dr. A. C. White for advice and cooperation, to Mesdames E. P. Penson and I. A. Saunders who carried out most of the pharmacological tests, to Mr. P. A. Young for statistical analyses and to Mr. P. R. W. Baker for the chemical analyses.

REFERENCES

1. Pohl, *Z. exp. Path. Ther.*, 1915, **17**, 370.
2. von Braun, *Ber. dtsch. chem. Ges.*, 1916, **49**, 977.
3. von Braun and Siddiqui, *ibid.*, 1926, **59B**, 1081.
4. McCawley, Hart and Marsh, *J. Amer. chem. Soc.*, 1941, **63**, 314.
5. Weijlard and Erickson, *ibid.*, 1942, **64**, 869.
6. Unna, *J. Pharmacol.*, 1943, **79**, 27.
7. Hart and McCawley, *ibid.*, 1944, **82**, 339.
8. Clark, Pessolano, Weijlard and Pfister 3rd, *J. Amer. chem. Soc.*, 1953, **75**, 4963.
9. Green and Young, *Brit. J. Pharmacol.*, 1951, **6**, 572.
10. von Mering, *Merck's Jahresb.*, 1898, **1**, 5.
11. Hesse, *Liebigs Annalen*, 1883, **222**, 206.
12. von Braun, *Ber. dtsch. chem. Ges.*, 1914, **47**, 2312.
13. Weil and Rosenblumowna, *Roczniki Chemji*, 1934, **14**, 1309.
14. Speyer and Walther, *Ber. dtsch. chem. Ges.*, 1930, **63**, 852.