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# STRUCTURE–ACTIVITY RELATIONSHIPS IN STEROIDAL ANAESTHETICS

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SUMMARY

Many steroids have been shown to possess anaesthetic activity and the properties which led to the selection of a mixture of 3α-hydroxy-5α-pregnane-11,20-dione (Alphaxalone) and 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione for clinical use are described. Further studies have revealed that the introduction of double bonds and substituents into Alphaxalone modify its anaesthetic activity, as determined in mice, and these modifications are discussed with particular reference to the conformation of the A-ring. A variety of side chains may be present at the 17β-position. Some water-soluble steroids which show instantaneous induction of anaesthesia are described.

## INTRODUCTION

The history of steroid anaesthesia began with Hans Selye's observations that the hormone progesterone showed anaesthetic activity [1] and that a metabolite of progesterone, 5β-pregnane-3,20-dione, showed greater activity [2]. Formulation of a therapeutically useful steroidal anaesthetic was achieved by a group at Pfizer [3], who studied structure-activity relationships in a series of water-soluble steroids [4]. The sodium succinate of 21-hydroxy-5β-pregnane-3,20-dione (Hydroxydione) (I)* dissolved in water to give a somewhat unstable solution for intravenous injection. Its main deficiencies were that it was of low potency, gave slow induction of anaesthesia, and showed a tendency to cause thrombophlebitis.

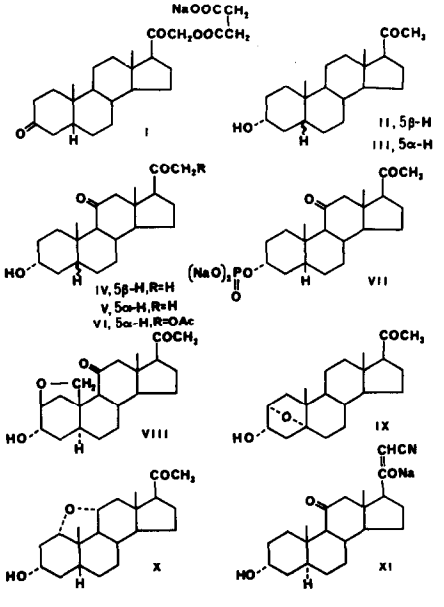


Fig. 1. Structures.

* Compounds are shown with Roman numerals and are displayed in Fig. 1 and Tables 1–4.

A comprehensive review [5] and work from Syntex [6] and our own laboratories [7] demonstrated that water-soluble derivatives of steroidal anaesthetics were usually less active and slower-acting than the alcohol or ketone from which they were derived. Three of the most active steroids were 3α-hydroxy-5β-pregnan-20-one (II), 3α-hydroxy-5β-pregnane-11,20-dione (IV) and 3α-hydroxy-5α-pregnane-11,20-dione (V). The best water-soluble compound from our own work appeared to be the 3-disodium phosphate (VII) of (IV). This gave stable aqueous solutions and although it did not induce anaesthesia instantly it did not cause thrombophlebitis. It was anaesthetic in man, but caused unexpected paraesthesia [8].

The next major step lay in dissolving water-insoluble steroids for intravenous injection in a biologically acceptable medium containing Cremophor EL (a polyoxyethylated castor oil made by Badische Anilin und Soda-Fabrik A.G), the non-ionic surface-active agent previously employed in the non-steroid intravenous anaesthetic Propanidid. The solubility in aqueous Cremophor EL of 3α-hydroxy-5α-pregnane-11,20-dione (Alphaxalone) (V), selected from our earlier studies of suspensions [7] was considerably improved by adding a second steroid, the less active 21-acetoxy-derivative (Alphadolone acetate) (VI). In this way, the formulation in 20 per cent Cremophor EL in water, known as Althesin, was achieved [9]. A report on its pharmacological properties in animals [10] was followed by a conference of steroid anaesthesia covering its pharmacology, clinical pharmacology, and clinical assessment [11]. The formulation gives instantaneous induction of anaesthesia and causes neither thrombophlebitis nor paraesthesia. It produces surgical anaesthesia of moderate duration, has a high therapeutic ratio and is compatible with common pre- and post-anaesthetic medicaments as well as inhalational anaesthetics.

We have continued to work in this area, with the goal of identifying steroids more active, less toxic, or giving an even better quality of anaesthesia than

Table 1. Ring A. Modifications of 3α-hydroxy-5α-pregnane-11,20-dione (V)
Sleep times (min)

| Compound No. | Modification | Dose (mg/kg) 1.6 | 3.1 | 6.3 | 12.5 | 25 | 50 | 100 |
|---|---|---|---|---|---|---|---|---|
| V | | | 3 | 6 | 17 | 27 | | |
| XXIII | 3β-$CH_3$ | | 1 | 6 | 14 | 22 | | |
| XXIV | 3β-$CH_2CH_3$ | | | | 1 | 10 | | |
| XXV | 2α-$CH_3$ | | 2 | 4 | 12 | 31 | | |
| XXVI | 2α-Br | | | | | 2 | | |
| XXVII | 2β-Mor | | | | | 17 | | |
| XXVIII | 2β-F | | | | 13 | | | |
| XXIX | 2β-Cl | 1 | 3 | 10 | | | | |
| XXX | 2β-Br | | 7 | 12 | 26 | | | |
| XXXI | 2β-I | | 4 | 18 | 43 | | | |
| XXXII | 2β-SCN | | 3 | 15 | 31 | 46 | | |
| XXXIII | 2β-OH | | | | | | | 12 |
| XXXIV | 2β-$OCOCH_3$ | | | 3 | 8 | 23 | 29 | |
| XXXV | 2β-$OCOCH_2CH_3$ | | | 7 | 12 | 18 | | |
| XXXVI | 2β-$OCH_3$ | | 5 | 15 | 45 | | | |
| XXXVII | 2β-$OCH_2CH_3$ | 4 | 9 | 22 | 35 | | | |
| XXXVIII | 2β-$OCH_2CH_2CH_3$ | 5 | 20 | | | | | |
| XXXIX | 2β-$OCH(CH_3)_2$ | 3 | 8 | 27 | | | | |
| XL | 2β-$OCH_2CH_2CH_2CH_3$ | 6 | 9 | 42 | 50 | | | |
| XLI | 2β-$OC(CH_3)_3$ | | | 4 | 17 | | | |
| XLII | 2β-$CH_3$ | 2 | 4 | 14 | 24 | | | |
| XLIII | 2β-$CH_2CH_2CH_2CH_3$ | 5 | 27 | | | | | |
| XLIV | $\Delta^1$ | | 1 | 2 | 7 | 12 | 23 | |
| XLV | $\Delta^4$ | | 1 | 5 | 8 | 15 | 24 | 35 |

Mor = Morpholino

Althesin. Although aqueous Cremophor EL appears quite acceptable as a pharmaceutical medium for intravenous use, other than in dogs where it evokes an anaphylactoid response, we have nevertheless continued to search for an effective water-soluble steroid, preferably stable in solution. Such a compound must possess the property of instantaneous induction of anaesthesia and lack irritant, thrombophlebitic, and paraesthetic effects, unlike earlier water-soluble steroids. To this end, we have prepared and tested more than a thousand steroids in our current programme.

## METHODS

The compounds have been examined by the intravenous route in male mice of the A2G, ICI or CDI strains, which all showed similar sensitivity, usually in groups of five. The steroids were given as solutions or suspensions in 20% Cremophor EL, unless they were soluble in water, the doses being successively halved from 200 mg/kg down to an ineffective level. Immediately after injection, the mice were placed in a cabinet maintained at 35°C. The time between injection and the loss of "righting reflex" was recorded as the induction time and the duration of loss of "righting reflex" was recorded as the sleep time. Deaths and signs of thrombophlebitis were recorded after 24 h.

In the tables, the activities are shown in simplified form. Thus each column represents one dose level of a group of five mice. If all five mice lost their righting reflexes without an induction period and all of them survived, the "sleep time" in minutes is recorded. Thus for example with Alphaxalone (V), the sleep times after instantaneous induction of anaesthesia were 3, 6, 17 and 27 min at doses of 3·1, 6·3, 12·5 and 25 mg/kg. Above 25 mg/kg one or more mice died. Below 3·1 mg/kg, either not all of the mice slept or there was a significant induction time.

## RESULTS AND DISCUSSION

In selecting compounds for discussion in this paper, I have concentrated on analogues of 3α-hydroxy-5α-pregnane-11,20-dione (Alphaxalone) (V). Introduction of extra hydroxyl groups at the 2α-, 4β-, 7β-, 9α-, 16α-, 16β- or 17α-positions resulted in inactive compounds and at the 2β- or 21-positions in the less

Table 2. Modifications of 3α-hydroxy-5α-pregnane-11,20-dione (V)
Sleep times (min)

| Compound No. | Modification | Dose (mg/kg) 1.6 | 3.1 | 6.3 | 12.5 | 25 | 50 | 100 |
|---|---|---|---|---|---|---|---|---|
| XLVI | $\Delta^5$ | | | | | | 5 | 20 |
| XLVII | $\Delta^8$ | | | 1 | 4 | 10 | | |
| XLVIII | $\Delta^{14}$ | | | | | 13 | 25 | |
| XLIX | 19-nor | | 3 | 4 | 8 | 17 | 22 | 37 |
| L | 19-nor, 2β-$OCH_2CH_3$ | | | 5 | 10 | | | |
| LI | 21-OH | | | | 6 | 11 | 21 | |
| VI | 21-$OCOCH_3$ | | | | 5 | 17 | | |
| LII | 21-$SCOCH_3$ | 1 | 5 | 9 | 16 | 38 | | |
| LIII | 21-$OCH_3$ | | | 1 | 5 | 13 | 23 | 41 |
| LIV | 21-$CH_2CH_3$ | | 1 | 8 | 19 | | | |
| LV | 21-cyclopropyl | | 1 | 8 | 14 | 27 | 47 | |
| LVI | 21-F | | 0.5 | 4 | 6 | 10 | | |
| LVII | 21-$N_3$ | | 1 | 6 | 13 | 24 | | |
| LVIII | 21-CN | | | | 7 | 21 | 37 | |
| XI | LVIII, Na salt* | | | | 1 | 6 | 18 | |
| LIX | 2β-$OCOCH_2$-Pip | | | | | 9 | 15 | |
| LX | 2β-$OCH_2CH_2$-Mor | | | | | | 2 | 23 |
| LXI | 21-$OCOCH_2N(CH_2CH_3)_2$ | | | | 0.5 | 6 | 15 | |
| LXII | 21-$SCSOCH_2CH_2$-Mor | | | | 6 | 17 | 40 | |
| LXIII | 21-$SCOCH_2$-Mor | | 3 | 8 | 26 | | | |
| LXIV | 21-Mor | | | | | 3 | 12 | 22 |
| LXV | LXIV, citrate* | | | | | 1 | 11 | 20 |
| LXVI | 2β-$OC_2H_5$, LXV* | | | | 2 | 9 | 23 | |

* in water.
Mor = Morpholino
Pip = Piperidino

active compounds (XXXIII and LI) respectively. Compounds lacking the 3α-hydroxyl but with a 2α-, 2β- or 3β-hydroxyl were inactive. Introduction of extra carbonyl groups at the 7- or 16-positions also destroyed activity.

The essential nature of the 3α-hydroxyl group was emphasised by the inactivity of compounds in which it was replaced by a 3α-mercapto, amino, morpholino, azido, chloro, or nitro-group. Derivatization of the 3α-hydroxyl, for example as esters, normally gave compounds with less activity and long induction periods. In the 5α-series, unlike the 5β-series, 3-ketones are not usefully active.

11-Deoxy-compounds are more readily available than 11-ketones, from diosgenin, solasodine or stigmasterol, but in general they have been poorer in activity than the 11-ketones—for example the parent 3α-hydroxy-5α-pregnan-20-one (III) gives slower induction and greater toxicity than Alphaxalone. Introduction of carbonyl groups at the 6- or 12-positions removed activity completely and at the 7-position (LXVII) considerably reduced it. Potency was also lessened by 11α- (LXVIII), 11β- (LXIX) or 21- (LXX) hydroxyl groups, along with toxicity, and eliminated by a 19-hydroxyl group.

Induction of a 3β-methyl group (XXIII) into Alphaxalone turns the compound from a secondary into a tertiary alcohol; this would prevent oxidation to 3-ketone and it might also slow the rate of formation of conjugates of the 3α-hydroxyl group. The activity, however, was virtually unaffected. Groups larger than methyl, for example in the ethyl compound (XXIV), tend to reduce the activity.

In the rat, Alphaxalone is metabolized in part to the inactive 2α-hydroxy analogue, probably as a glucuronide [12] and the effect of substitution at the 2-position is therefore of particular interest. However, a 2α-methyl group (XXV), which may block 2α-hydroxylation, did not affect activity in the mouse. In case metabolism differed in the mouse and rat, the activity was checked in the rat and again found to be close to that of Alphaxalone [9]. Introduction of a 2α-bromine atom (XXVI), on the other hand, reduced activity in the mouse.

The introduction of a variety of substituents at the 2β-position has shown that quite large groups can be introduced, sometimes with an improvement in activity. The 2β-morpholino compound (XXVII) has been previously described by workers at Organon [13] as causing loss of righting reflex in

Table 3. Modifications of 3α-hydroxy-5α-pregnan-20-one (III)
Sleep times (min)

| Compound No. | Modification | Dose (mg/kg) 3.1 | 6.3 | 12.5 | 25 | 50 | 100 | 200 |
|---|---|---|---|---|---|---|---|---|
| III | - | | 18 | | | | | |
| LXVII | 7 = O | | | | | 13 | 23 | |
| LXVIII | 11α-OH | | | | | 19 | 41 | 64 |
| LXIX | 11β-OH | | | | | 19 | | |
| LXX | 21-OH | | | 11 | 37 | | | |
| LXXI | $\Delta^1$ | | 10 | 18 | 43 | 55 | | |
| LXXII | $\Delta^4$ | | 5 | 8 | 22 | 36 | | |
| LXXIII | $\Delta^5$ | | | 2 | 13 | 19 | | |
| LXXIV | 2β-$OCH_3$ | 2 | 29 | | | | | |
| LXXV | 2β-$OCH_3$, $\Delta^4$ | | | | 11 | 20 | 44 | |

Table 4. Modification of 3α-hydroxy-5α-androstan-11-one.
Sleep times (min)

| Compound No. | Modification | Dose (mg/kg) 3.1 | 6.3 | 12.5 | 25 | 50 | 100 | 200 |
|---|---|---|---|---|---|---|---|---|
| LXXVI | 17β-$C_2H_5$ | | | | 37 | 45 | | |
| LXXVII | 17β-$CO_2CH_3$ | | 1 | 14 | 31 | | | |
| LXXVIII | 17β-$CO_2C_2H_5$ | | | 4 | 12 | 35 | 57 | |
| LXXIX | 17β-$COCH_3$ | | | 10 | 22 | 37 | | |
| LXXX | 17β-$CON(CH_3)_2$ | | | 1 | 6 | 23 | | |
| LXXXI | 17β-CN | 0.5 | 6 | 11 | 26 | | | |
| LXXXII | 17β-$CO_2CH_2CH_2$-Mor | | | | | 6 | 24 | 39 |
| LXXXIII | 2β-$OC_2H_5$, LXXXII | | | 1 | 6 | 12 | | |
| LXXXIV | LXXXIII, citrate* | | | 1 | 7 | 12 | | |
| LXXXV | 17β-$COCH_2CH_2$-Mor | | | 6 | 9 | 34 | | |

* in water
Mor = Morpholino

mice; our assay shows that it is considerably less active in this respect than Alphaxalone with about the same toxicity. The small electronegative fluorine substituent (XXVIII) also has a deleterious effect on activity but the larger halogens, chlorine (XXIX), bromine (XXX), and iodine (XXXI), or a thiocyanato-group (XXXII), all gave products with good activity. the chloro-compound being active at one dose lower than Alphaxalone.

Although substitution with a 2β-hydroxyl gave a weakly active compound (XXXIII), esterification of the 2β-hydroxyl as acetate (XXXIV) or propionate (XXXV) almost completely regenerated the activity, indicating that the esters are acting as such and are not readily hydrolysed. The 2β-ethers (XXXVI to XL), more stable than esters, were particularly active, giving longer sleep times at 3·1 mg/kg than Alphaxalone. In four instances they were active at half of this dose, the best compounds being the ethoxy (XXXVII) and n-butoxy (XL) derivatives. The isopropoxy compound (XXXIX) was less toxic than the n-propoxy-compound (XXXVIII) and it is interesting that activity was retained in the presence of a bulky t-butoxy substituent (XLI).

2β-Alkyl compounds are more difficult to prepare, but again the 2β-methyl derivative (XLII) was twice as active; the 2β-n-butyl derivative (XLIII) gave even longer sleep times but was more toxic.

Substitution on the other side of the 3α-hydroxyl group, at the 4β-position, with a variety of groups, surprisingly gave compounds almost devoid of activity.

Previous structure-activity relationship studies [6] concluded that the introduction of double bonds at the 4,5- or 5,6-positions resulted in compounds with negligible anaesthetic activity, but this was based solely on the poor activity of $\Delta^4$-3-ketones and $\Delta^5$-3β-ols. On the contrary, we have found that with 3α-ols introduction of double bonds into ring A reduces toxicity, particularly in the 11-deoxy series. Thus, in the 11-deoxy series, 3α-hydroxy-5α-pregnan-20-one (III), active at one dose, is more toxic than the $\Delta^1$- (LXXI) or $\Delta^4$- (LXXII) compounds, active at four doses. In the corresponding 11-ketones, Alphaxalone (V) is active over four doses whereas the $\Delta^1$- (XLIV) and $\Delta^4$- (XLV) compounds are active over five and six doses respectively. The introduction of a 5,6-double bond was less satisfactory, but it is interesting to find that the 11-deoxy-compound (LXXIII) was

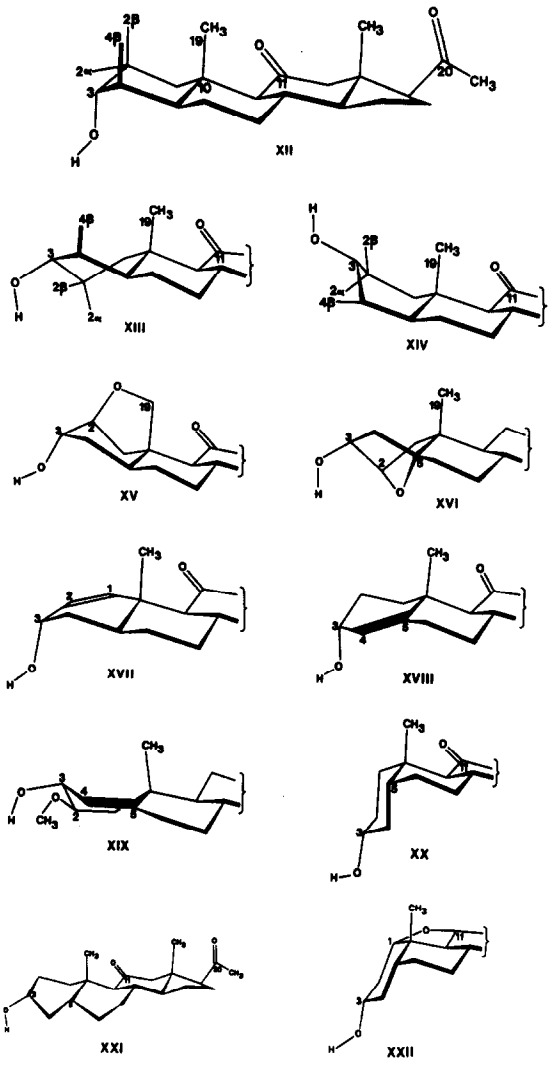


Fig. 2. Conformations.

better than the 11-ketone (XLVI). An 8,9-double bond (XLVII) reduced activity somewhat, a 14,15-double bond (XLVIII) more so and a 16,17-double bond completely.

Consideration of the effect of ring A substituents and double bonds led us to speculate that the conformation, that is, shape, of ring A may be of importance.* In 5α-pregnanes, the normal conformation is with rings A, B and C as chairs (Fig. 2, XII) and indeed the proton magnetic resonance spectra of most of our compounds would support this. However, such spectra are taken in solution in deuteriochloroform and may not be entirely relevant to the biological situation. Ring A can change conformation, without affecting the shape of the rest of the molecule, into two boat forms, trivially called the "α-boat" (XIII) and the "β-boat" (XIV) [14]; there is also a "twist" form intermediate between the boats. Thus it might be expected that a 2β-substituent, such as a methyl group, in a 1,3-diaxial relationship with the angular methyl group, would tend to drive ring A towards the "α-boat" in which such interaction is diminished, and that such a conformation may be the one associated with activity. On the other hand, introduction of a 4β-substituent, such as a methoxy group, would tend to drive ring A towards the "β-boat", which is perhaps an inactive conformation.

To challenge this theory, we prepared the 2β,19-oxide (VIII), in which ring A is held in the chair form (XV); the 2β-position can be regarded as carrying an intra-molecular alkoxy substituent. As forecast, this compound was inactive.

Removal of the angular methyl group from C-10 in Alphaxalone gives the corresponding 19-nor-compound (XLVIII) which is just as active but less toxic. It was therefore of interest to prepare the 2β-ethoxy-19-nor compound (XLIX), for in this there cannot be a large 1,3-diaxial interaction between substituent and angular methyl. Again, as predicted, there was no gain in activity, instead there was rather a loss.

In an attempt to fix ring A in the "α-boat", we prepared the 2α,5α-oxide in the 11-deoxy-series (VIII, XVI). This, however, proved to be inactive, but perhaps because the oxide bridge projects on the α-face of the molecule.

The conformations (XVII and XVIII) taken up by $\Delta^1$- (XLIV) and $\Delta^4$- (XLV) compounds are similar to that of the "α-boat" (XIII), in terms of the hydroxyl position. In the 11-deoxy series, we examined the effect of combining a 2β-methoxy substituent with a 4,5-double bond and this combination (LXXV) proved worse than the individual modifications (LXXII) and (LXXIV). Although, in deuteriochloroform, the compound clearly exists with the methoxy group axial, if the 2β-group is repelled the resulting conformation is quite unlike the "α-boat", the hydroxyl moving onto the β-face of the molecule (XIX).

If the shape of ring A is indeed so important, it is surprising that compounds of the 5α- and 5β-series show similar activity as they are greatly different in shape in the all-chair conformations (XII) and (XX). The only conformation in which the 5β-isomer carries the hydroxyl in roughly the same position as in the 5α-series, is the energetically highly unfavoured one (XXI) with both the A and B rings as boats—perhaps we should call this a catamaran!

Both 11-oxo (IV) and 11-unsubstituted (II) compounds are active in the 5β-series and so if an all-chair conformation is the effective one then the 1α,11α-oxide (X, XXII) should be active—it cannot assume the catamaran conformation. It was found inactive, which leaves the catamaran theory still afloat.

Turning to the other end of the molecule, substitution at the well-tried 21-position has also proved rewarding. The 21-hydroxy-compound (LI) and its acetate (VI) (Alphadolone acetate, the minor component of Althesin) both retain moderate activity. In contrast, the 21-thio is active only at toxic doses whereas the acetyl-thiol-derivative (LII) is more active than Alphaxalone and no more toxic. 21-Alkoxy-compounds, for example the 21-methoxy-compound

* Conformations are shown in Fig. 2.

(LIII), showed reasonable activity, as did compounds with an extended alkyl side chain, for example the 21-ethyl-compound (LIV). The 21,21-ethylidene derivative (LV), in which the original 21-carbon atom forms part of a cyclopropane ring, was as active as Alphaxalone but less toxic. Fluorination at the 21-position (LVI) had little effect on activity, but larger halogens were less satisfactory. An azido-substituent (LVII) had little effect on activity, but did show the property of considerably enhancing solubility in 20% Cremophor EL.

A 21-cyano-substituent (LVIII) reduced the activity but the compound was of particular interest in that it was weakly acidic. Thus, although we had not found any steroidal carboxylic acids with useful activity, this compound was sufficiently acidic to give a sodium enolate (XI), soluble in water with fair stability. Furthermore, the aqueous solution of sodium salt showed virtually the same activity as did the parent compound in 20% Cremophor EL. Although the solution was rather alkaline, pH 11·7, there were no indications of thrombophlebitis in mice.

Having shown that the 2$\beta$- and 21-positions could carry large substituents, we prepared a series of compounds with a basic nitrogen atom within the substituent, which are therefore likely to give water-soluble salts. For example, the 2$\beta$-piperidinoacetate (LIX) showed instantaneous induction of anaesthesia but was much less active than the corresponding 2$\beta$-acetoxy-compound (XXXIV). Its citrate was soluble in water and showed similar potency. The 2$\beta$-morpholinoethoxy-compound (LX) was disappointingly less active than the 2$\beta$-ethoxy-compound (XXXVII). The 21-diethylaminoacetoxy derivative (LXI) and the xanthate (LXII) were reasonably effective, but for the first time in a potentially water-soluble compound we reached activity comparable to that of Alphaxalone with the 21-morpholino-acetylthio-derivative (LXIII). This showed similar activity in aqueous solution as its hydrochloride, but as with the 21-diethylaminoacetate (LXI) and the xanthate (LXII), it was somewhat unstable in aqueous solution.

Direct substitution at the 21-position with various amines gave a more stable group of compounds. Those with a free NH group were inactive; the best compounds were those substituted by heterocyclic amines, for example morpholine or thiomorpholine. The morpholino-compound (LXIV) showed reasonable activity and this was maintained in aqueous solution as its citrate (LXV). Substitution with a 2$\beta$-ethoxy-group (LXVI) doubled the activity; similar activity was shown by other salts such as the acetate or ascorbate.

All of the compounds so far described here have been pregnan-20-ones, that is they have a 17$\beta$-acetyl side chain. Compounds with a 17$\alpha$-acetyl side chain show at best weak activity. Reduction of the 20-carbonyl to a 20$\alpha$- or 20$\beta$-hydroxyl group destroys activity, and complete reduction gives the 17$\beta$-ethyl compound (LXXVI) with only weak activity.

Insertion of an oxygen atom between C-17 and C-20 gives the inactive 17$\beta$-acetoxy-compound but we were pleased to find that insertion of an oxygen atom between C-20 and C-21 reduced potency only slightly. This compound is the 17$\beta$-carboxylic acid methyl ester (LXXVII), the acid itself being inactive. Esters with other alcohols, for example the ethyl ester (LXXVIII), or thiols, for example the methylthiocarbonyl-compound (LXXIX), also showed activity. The dialkylamides, such as the dimethylamide (LXXX) are active but monoalkylamides were less effective and the amide was inactive. Dehydration of the amide gave the nitrile (LXXXI) which was very close in activity to Alphaxalone.

The esters of the carboxylic acid have also provided water-soluble derivatives with good stability in aqueous solutions attributable to steric hindrance. The morpholino-ethyl ester (LXXXII) showed fair activity and this could be maintained in compounds with larger alkyl chains in the ester group. Further, introduction of a 2$\beta$-ethoxy group (LXXXIII) improved the activity and this was retained in aqueous solutions of the citrate (LXXXIV) and other salts such as the hydrochloride, lactate, ascorbate, phosphate, or methanesulphonate. Improved activity also came with the ester of morpholino-ethanethiol (LXXXV).

In conclusion, we have shown that improved activity or reduced toxicity can be achieved and that it is possible to obtain a variety of water-soluble compounds which give instantaneous induction of anaesthesia and which do not show untoward effects such as thrombophlebitis in mice. Many combinations of groups are possible, and our experience so far is that it is still difficult to forecast activity with accuracy. It must be emphasized that these results are only in mice and it remains to be seen whether any of the compounds will prove to be an improvement on Althesin.

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