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AN EFFICIENT SYNTHESIS OF N-CYCLOBUTYLMETHYLNOROXYMORPHONE FROM THEBAINE†

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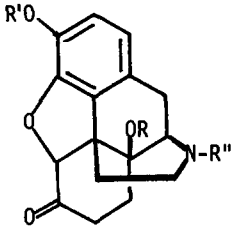
The search for a safe, effective, and nonaddictive replacement for morphine for the treatment of severe pain has occupied scientists for over a hundred and fifty years. A most promising recent discovery in this area is N-cyclobutylmethylnoroxymorphone (nalbuphine = 1), an analgesic now undergoing extensive clinical evaluation. A mixed agonist-antagonist drug, nalbuphine is reported to be as potent an analgesic as morphine and 2-5 times as active a narcotic antagonist as nalorphine.[1] Similar claims[2,3] have been made for other 3,14-dihydroxy-N-cyclobutylmethylmorphinans including the parent compound (butorphanol), " a highly potent dependence free agonist..."[2]



1: R = R' = H, R" = CH_2-Cyclobutyl (nalbuphine)
2: R = H, R' = R" = Methyl (oxycodone)
3: R = R' = H, R" = Methyl (oxymorphone)
4: R = R' = Acetyl, R" = Methyl
5: R = R' = Acetyl, R" = Cyano
6: R = R' = R" = H (noroxymorphone)

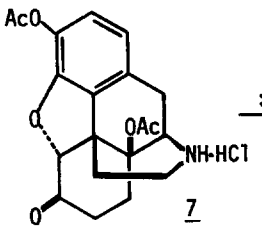
Nalbuphine is presently made[4] from the alkaloid, thebaine, via the commercial analgesic, oxycodone (2), and its O-demethylation product, oxymorphone (3). The latter is O,O-diacetylated (→4), then N-demethylated with BrCN (→5), and subsequently stripped of the cyano and acetyl residues with strong acid to give noroxymorphone (6). Here the preferred synthesis of 1 deviates from the commercial route to naloxone[5] (N-allylnoroxymorphone) because cyclobutylcarbinyl bromide unlike allyl bromide is a very poor alkylating agent.[6] Instead the N-cyclobutylmethyl moiety is attached by N-acylation followed by LAH reduction of an intermediate

†Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

N-cyclobutylcarbonyl species. To protect and reconstitute the phenol and keto functions, extra steps were incorporated in the published schemes.[4] For the transformation, noroxymorphone (6) → nalbuphine, 50% would be a most optimistic estimate[7] of the best lit. yield, a value even less palatable when multiplied by 37%, the best reported yield for the conversion, oxycodone → 6.[5,8]

Attempts to prepare nalbuphine from oxymorphone using vinyl chloroformate (VOC-Cl) for N-demethylation and hydroxyl protection as in the nalorphine synthesis already outlined[9] were not very satisfactory. Reaction at the 14-OH was not complete (and could not be avoided entirely). Moreover, the 14-O-VOC material behaved anomalously in base. A study of the neutralization of 3,14-diacetylnoroxymorphone hydrochloride[5] (7) exposed the problem - and revealed its solution. Treatment of the HCl salt (7) with an equivalent of $NaHCO_3$ or Et_3N yielded not the free amine but the rearranged amide (8). This geometrically favored, intramolecular O→N acyl transfer occurred spontaneously on liberation of the amine and is essentially instantaneous at 20°.[10]

IR(μ) in CH_2Cl_2:
3.5-4.1 (m)
5.67 (s)
5.72 (sh)
5.74 (s)



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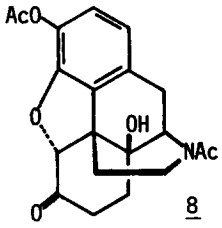
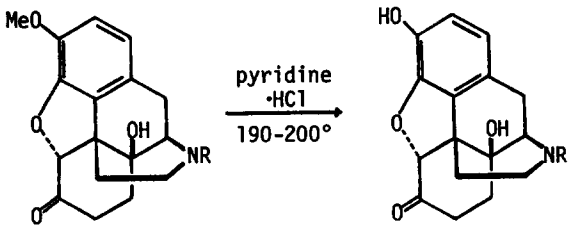


8

IR(μ) in CH_2Cl_2:
2.9-3.15 (m)
5.65 (s)
5.74 (s)
6.1-6.25 (s)

The incompatibility of a secondary amino function with a 14-acyloxy group in the morphinan system imposed severe limitations on the kinds of phenol protection permitted during a nalbuphine synthesis. Most attractive to us was a strategy in which the O-methyl of oxycodone (2) was retained until after attachment of the N-cyclobutylmethyl group, a scheme which would require that the latter be at least as stable as the N-methyl of oxycodone to the conditions of O-demethylation. As is evident from the following data, results exceeded expectations:



Rxn.	R=	Found Yield	Corr.[a] Yield
A:	Methyl	65% (+4%[b])	74%
B:	CH_2-◇	71% (+4%[b])	80%
C:	Allyl	40% (+6%[b])	42%

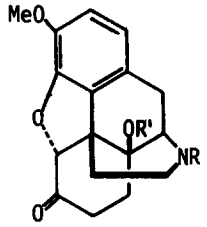
[a] for recovered starting material
[b] in filtrate; not in corr. yield

The O-demethylation of oxycodone (rxn. A), which was reproduced in the best lit. yield (74% vs. 75%[8]), was substantially worse than the O-demethylation of the N-cyclobutylmethyl compound (B). However as anticipated, an N-allyl unit destabilized the system (C), so any such route devel-

oped for the preparation of 1 could not usefully be extended to the production of naloxone.

When combined with the use of VOC-Cl for N-demethylation, the just described acyl shift and O-demethylation strategy provided the keys to a very efficient synthesis of nalbuphine:

First, oxycodone (2) was converted in quantitative yield to its 14-cyclobutylcarbonyl derivative (9) by treatment with cyclobutanecarboxylic acid anhydride[11] in dioxane at 100°.



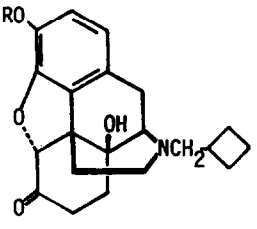
			IR (μ) in CH_2Cl_2:
2:	R = Methyl, R' = H	(oxycodone)	2.9-3.0 [m], 5.78 [s]
9:	R = Methyl, R' = 	mp 151°[12]	5.73-5.91 [s]
10:	R = VOC, R' = 	amorph	5.71-5.92 [s], 6.08 [m]
11:	R = H·HCl, R' = 	mp 217° d	3.5-4 [m], 5.73-5.82 [s]
12:	R =  , R' = H	foam	2.9-3.1 [m], 5.78 [s], 6.1-6.3 [s]

Next, the crude 9 was N-demethylated with VOC-Cl in 1,2-dichloroethane at 65° to give the N-VOC compound (10) isolated as a white foam in 94% yield (from 2). Unreacted 9 (5%) was also recovered in the extraction work-up. Removal of the VOC group was cleanly accomplished by bubbling anhydrous HCl through 10 in CH_2Cl_2 followed by evaporation and subsequent dissolution of the intermediate adduct in hot methanol.[9] The O-acylnoroxycodone hydrochloride (11) thus obtained as a white solid was dissolved in CH_2Cl_2 and shaken with aqueous $NaHCO_3$. As expected, immediate, quantitative rearrangement to the N-acylnoroxycodone (12) occurred.

Having completed its initial function, protection of the 14-OH during N-demethylation, the cyclobutylcarbonyl moiety was ready to serve its second purpose. First the 6-ketone was masked by treatment of 12 with ethylene glycol and pTosOH (0.06 eq) in benzene at reflux. The product ketal (13) crystallized from benzene as a 1:1 adduct with the solvent, a substance which was very insoluble in cold benzene unlike other neutral intermediates, byproducts, and side products on the route from 2 to 13. This serendipitous result permitted the development of a process in which the product extraction residues or precipitates from each step in the scheme, 2 → → → 13, were used as the precursors for the next step without purification. The overall yield from 2 of pure 13 adduct obtained in this way was 86%.[13] Heating the adduct in vacuo at 90°

13: R = 
white needles
mp 192.5-193°

14 R = 



15: R = Methyl
mp 98-99°

1: R = H
(nalbuphine)

gave solvent-free 13. Reduction of the amide (13) to a cyclobutylmethylamine was achieved by reaction with excess LAH in THF. The amino ketal (14) was not isolated but hydrolyzed during acid workup to the amino ketone (15) which crystallized in 85% yield from ether-pentane. Finally, O-demethylation as already described afforded nalbuphine (1). The overall yield of pure, recrystallized nalbuphine from oxycodone was 58.4%. Based on thebaine,[14] the overall yield was 49% with potential for further improvement by workup of recrystallization filtrate residues.

The adaptation of this synthesis or parts thereof to the improved preparation of other 14-hydroxymorphinan pharmaceuticals (naltrexone,[1] oxilorphan,[2] etc.[1-4]) is easily envisaged.

Acknowledgement. We are grateful to the National Institutes of Health for the grant (GM 13980) which supported this research.

Footnotes and References

1) H. Blumberg, H. B. Dayton, and P. S. Wolf, Toxicol. Appl. Pharmacol., 10, 406 (1967); H. Blumberg and H. B. Dayton, Advan. Biochem. Psychopharmacol., 8, 33 (1973).

2) I. Monkovic, T. T. Conway, H. Wong, Y. G. Perron, I. J. Pachter, and B. Belleau, J. Amer. Chem. Soc., 95, 7910 (1973); I. Monkovic and T. T. Conway, U. S. Pat. 3,775,414, Nov. 27, 1973; A. W. Pircio and J.A. Gylys, J. Pharmacol. Exp. Ther., 193, 23 (1975).

3) S. Yoshiro, R. Maeda, and H. Tada, Japan Pat. 71 04, 169, Feb. 2,1971 [CA 75, 20226e (1971)].

4) H. Blumberg, I. J. Pachter, and Z. Matossian, U. S. Pat. 3,332,950, July 25, 1967.

5) For discussion and refs. see: R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, Second of preceding communications.

6) Even the simpler N-alkylation of noroxycodone with cyclobutylcarbinyl bromide gave N-cyclobutylmethylnoroxycodone in only 34% yield in our hands; several other products were also obtained. Cyclopentyl acetate is the main product from acetolysis of cyclobutylcarbinyl tosylate: K. B. Wiberg and B. A. Hess, J. Amer. Chem. Soc., 88, 4433 (1966). For other data see: A. P. Krapcho and R. G. Johanson, J. Org. Chem., 36, 146 (1971).

7) Yields are missing for key steps in published data.[4] In the two best schemes, the choice is between 72% plus missing yields in three subsequent steps or 49% plus a missing yield in a final Oppenauer oxidation.

8) I. Seki, Takamine Kenkyusho Nempo, 12, 56 (1960).

9) R. A. Olofson and R. C. Schnur, Preceding communication.

10) For similar rearrangement at high temperature during hydrolysis of N-cyano-14-hydroxynorcodeine derivatives see: A. C. Currie, G. T. Newbold, and F. S. Spring, J. Chem. Soc., 4693 (1961).

11) M. Freund and E. Gudeman, Chem. Ber., 21, 2692 (1888). This has no economic disadvantage since the carboxylic acid is the normal precursor of the cyclobutylmethyl bromide.

12) Satisfactory combustion analyses and corroborative IR, NMR, and high resolution mass spectral data have been obtained for all new compounds including 10 and 12 (but not 14).

13) Another 2-3% of 13 was present in the final crystallization filtrate, accounting for ca 25% of the residue.

14) Assuming 88% yield for the conversion of thebaine to 14-hydroxycodeinone with H_2O_2 in formic acid [I. Seki, Takamine Kenkyusho Nempo, 12, 52 (1960)] and 94% yield for the subsequent hydrogenation to oxycodone.