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Narcotic Antagonists. V. Stereochemistry of Reactions at C-6 in 14-Hydroxynoroxymorphone Derivatives

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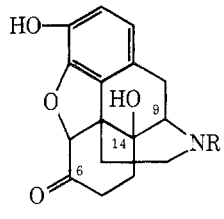
The epimeric products of the borohydride reduction and of the methyllithium reaction of the C-6 ketone of naloxone were isolated. The stereochemistry of the products was assigned on the basis of nmr evidence, which indicates that in each case the major product has the 6α-hydroxy orientation.

The retention of varying degrees of agonist character in virtually all of the presently known narcotic antagonists serves to limit their clinical utility. Striking exceptions are the structurally related compounds naloxone (Ia) and naltrexone (Ib) which exhibit minimal agonist activity. This

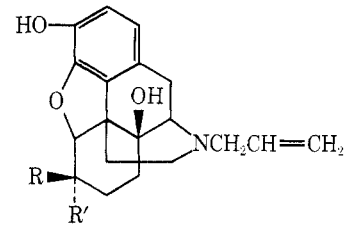


Ia, R = $CH_2CH{=}CH_2$
b, R = CH_2— 

has led to the clinical use of naloxone for the reversal of narcotic-induced effects and to the present clinical evaluation of naltrexone as a potential prophylactic agent in narcotic addiction.[1] In the course of their clinical evaluation, the metabolism of these compounds in man has been investigated and it showed that their principal transformation *in vivo* is the reduction of the 6-ketone group.[2] The report that naltrexone, unlike naloxone, gives rise to a reduced metabolite with the C-6 isomorphine configuration,[3] and that this metabolite may be responsible for its long duration of action in man,[4,5] has aroused our interest in the stereochemistry of reactions at that functional center since the epimeric relationship of their metabolites may have bearing on the difference in properties of the two drugs.

A structural feature common to both naloxone and naltrexone is the 14β-hydroxyl group which may influence the course of reaction at the C-6 position and give products with an orientation different from those obtained from the more common morphine and codeine derivatives containing a hydrogen at the C-14 position.

Sodium borohydride reduction of the C-6 carbonyl group of Ia has been previously reported on by Dayton and Blumberg,[6] and the product was identified as the 6-hydroxy compound IIa which was shown to be identical with the principal metabolite of naloxone obtained *in vivo*.[2] The orientation of the 6-hydroxy group in IIa was assigned



IIa, R = H; R′ = OH
b, R = OH; R′ = H

as α by analogy to reductions of the 6-ketone in other morphine derivatives. There have been a number of other reports on the sodium borohydride reduction of the 6-ketone in 14-hydroxy morphine and codeine derivatives in which the orientation of the products was similarly assigned by analogy to 14-hydrogen compounds. These reactions included reduction of 14-hydroxycodeinone by Sargent, *et al.*,[7] and Currie, *et al.*,[8] and the reduction of 14-hydroxydihydromorphinone by Weiss and Daum.[9] Conclusive evidence for the stereochemistry of reduction in the model 14-hydrogen series has only recently been provided by Sargent and Jacobson.[10] They compared the nmr spectra of codeine and isocodeine and noted differences in the chemical shift of the 14-proton. In isocodeine it was deshielded by the β-hydroxyl group at C-6 because of its 1,4-diaxial relationship and appeared at δ 3.08. In the spectrum of codeine, where the C-6α-hydroxyl group is equatorially oriented, the 14-hydrogen resonance was at δ 2.66. The above nmr evidence of the interaction of the C-6 and C-14 substituent suggests that the presence of a 14β-hydroxyl group makes such an analogy to the 14-hydrogen series suspect as far as the C-6 ketone reduction products are concerned, and therefore the assigned stereochemistry of IIa and the other reduced products cannot be considered secure.

Naloxone was reduced quantitatively with borohydride and gave a mixture which by tlc analysis consisted of two compounds. The less polar IIa was the major product and was estimated to be nine times greater than the yield of the lesser and more polar product IIb. Preparative tlc permitted the isolation of a small quantity of each of the two components of the mixture. Oxidation of either IIa or IIb re-

generated naloxone confirming the epimeric nature of the two reduction products. The relationship between the two isomeric compounds was further established by chemical inversion of the major product IIa to the minor one IIb. Treatment of the 6α-hydroxy epimer of IIa with toluenesulfonyl chloride gave the tritosyl derivative at positions 3, 6 and 14 (III). This compound, when allowed to react with tetrabutylammonium acetate, and then 5% ethanolic potassium hydroxide,[11] gave the epimeric 6β-hydroxy compound IIb in low yield. A better source of IIb was attained by a separation of the mixture of C-6 epimers using high-pressure liquid chromatography. The compounds IIa and IIb isolated by this technique were indistinguishable from those obtained by the previous procedures.

Spectral data were used to assign the absolute configurations in IIa and IIb. The infrared spectra of both compounds showed no carbonyl absorption and only subtle differences between the spectra in the fingerprint region were apparent. The nmr spectra of the two compounds proved to be more informative. Product IIa showed a peak at δ 4.62 which was assigned to the 5β hydrogen and a broad resonance at δ 4.2–4.4 attributed to the 6β hydrogen. Compound IIb had a peak at δ 4.52 corresponding to the 5β hydrogen and a new broad absorption in the region δ 3.3–3.6, which we assign to the 6α hydrogen. These values were compared with the nmr data reported for dihydrocodeine and dihydroisocodeine[12] (Table I). The greater downfield

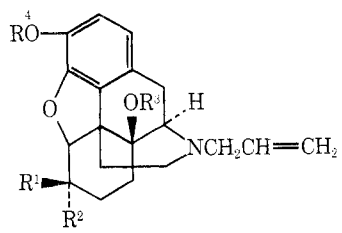
Table I[a]

Compd	5β-H	6α-H	6β-H
IIa[b]	4.62		4.2–4.4
IIb[b]	4.52	3.3–3.6	
Dihydrocodeine[c]	4.58		4.0–4.2
Dihydroisocodeine[c]	4.37	3.4–3.6	

[a] Spectra are reported in δ values. [b] Spectra were run in $CDCl_3$ using TMS as internal standard. [c] Spectra were obtained using cyclohexane as internal standard.

shift of the 5β hydrogen in IIb relative to that in dihydroisocodeine is a reflection of the difference in the angular relationship to the 6β hydroxyl because of the steric influence of the 14β hydroxyl. Also, the greater deshielding of the 6β hydrogen in IIa relative to dihydrocodeine is the result of the presence of the cis 14β-hydroxyl group.

Further support for the above stereochemical assignments was obtained from the nmr spectra of the acetate derivatives of IIa and IIb. The position of the 6-hydrogen absorption in 3,6-diacetates IVa and IVb is unchanged from



IVa, R^1 = H; R^2 = OAc; R^3 = H; R^4 = Ac
b, R^1 = OAc; R^2 = R^3 = H; R^4 = Ac
c, R^1 = H; R^2 = OAc; R^3 = R^4 = Ac
d, R^1 = OAc; R^2 = H; R^3 = R^4 = Ac

that in IIa and IIb. However, its position is shifted downfield to δ 4.5–4.8 (superimposed on the C-5 hydrogen) in 3,6,14-triacetate IVc. This effect is not noted in triacetate IVd, where the C-6-hydrogen absorption is unchanged. The downfield shift may be ascribed to a deshielding effect by the 14-acetate group in IVc, since it is cis to the 6β hydrogen. This situation does not exist in IVd where the 6α hydrogen is trans to the 14-acetate group. The new absorption at δ 4.35 in IVc and IVd is attributed to the 9α hydrogen, which has shifted downfield due to esterification of the 14β-hydroxyl group.

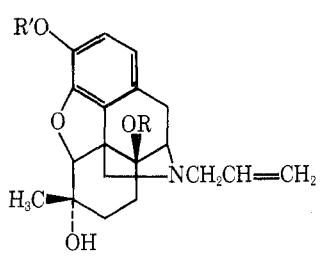
The position of acetate group absorption in IVa and IVb also confirms our assignments. In 3,6-diacetate IVa, the 6-acetate exhibits a peak at δ 1.80, while the 3-acetate absorbs at δ 2.28. In IVb, however, the position of absorption of the 6-acetate has shifted downfield to δ 2.08, while that of the 3-acetate is unchanged. This shift is a result of the 14-hydroxyl group interacting with the cis 6-acetate of IVb and it is absent in IVa where the groups are trans to one another.

The above data provide evidence that the stereochemistry of the borohydride reduction of the 6-keto group is only mildly affected by the presence of a 14β-hydroxyl function, in that it leads to the generation of a small amount of the 6β-hydroxy product, which is absent in the reduction of the 14-hydrogen series.[8,9]

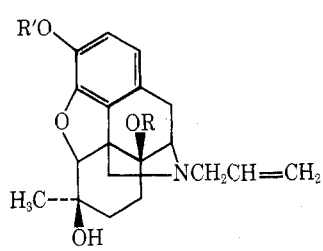
To examine the effect of the 14β-hydroxyl group on other sterically demanding reactions at the C-6 ketone group, we studied the C-6 methylation of naloxone, Ia. Reaction of Ia with methyllithium provided the 6β-methyl derivative Va, but the yield was moderate compared to the same reaction in the 14-hydrogen series.[13,14] When the reaction was carried out on a larger scale a small amount of the 6α-methyl isomer VIa was also isolated; the ratio of Va to VIa was 20:1. In an effort to improve the overall yield of the 6-methyl isomers, we reacted naloxone 3,14-diacetate[15] with methyllithium. In addition to naloxone and Va, compound Vb, the product of deacetylation at the more reactive position 3, was also isolated.

The stereochemistry of the isomeric 6-methyl derivatives was assigned using the nmr data which are presented in Table II. It is evident that changes at position 6 or 14 have

Table II[a]



Va, R = R′ = H
b, R = Ac; R′ = H
c, R = H; R′ = Ac



VIa, R = R′ = H
b, R = H; R′ = Ac
c, R = R′ = Ac

Compd	5-H	6Me	14-OAc(Me)	3-OAc(Me)
VIa	4.32	1.27		
Va	4.36	1.38		
VIb	4.34	1.23		2.29
Vc	4.35	1.30		2.31
VIc	4.38	1.21	2.15	2.31
Vb	4.34	1.30	2.06	

[a] Spectra were run in $CDCl_3$ using TMS as internal standard and are reported in δ values.

little effect on the C-5 proton. In VIa the C-6 methyl absorbs at δ 1.27 *vs.* δ 1.38 in Va. This agrees with the deshielding effect noted in the borohydride reduction products, IIa and IIb, *i.e.*, the methyl group cis to the 14-hydroxyl function absorbs at a lower frequency than the one

trans to it. A similar situation is observed in 3-acetate derivatives Vc and VIb. When comparing 14-acetate derivatives Vb and VIc, a deshielding is recorded for the 14-acetate methyl cis to the 6-hydroxyl group VIc, relative to that in Vb where a trans relationship exists. This data for the relative positions of these absorptions in the epimeric products correlate well with values observed in IIa and IIb and also with those in the report by Sargent and Jacobson who compare the nmr spectra of 6-methylcodeine and 6-methylisocodeine.[10] The latter comparison appears to be valid despite the relative flexibility of ring C in the dihydrocodeine *vs.* codeine structure. It should be noted that the 3-acetate of VIc does not influence the position of absorption of the 14-acetate group.[15]

The present work provides a secure stereochemical identification of the major and minor epimeric products of the borohydride reduction and the methyllithium reaction of the C-6 ketone in the 14β-hydroxy morphinone series. The major product in each case reflects predominant approach of the reagent from the β side yielding the 6α-hydroxy epimer in each case. This disproportionate preference for β side attack, despite the presence of the 14β-hydroxyl group, suggests that in the chair conformation of ring C,[12] α approach at C-6 is greatly hindered and the products of the reactions reflect steric approach control.

Experimental Section[16]

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine (IIa) and *N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine (IIb) by Sodium Borohydride Reduction of Naloxone.** Naloxone (63 mg, 0.2 mmol) was dissolved in ethanol (10 ml) and sodium borohydride (40 mg, 0.8 mmol) was added. The reaction was stirred at room temperature for 3 hr. Excess sodium borohydride was destroyed by the addition of a saturated solution of ammonium chloride, and the pH of the reaction was adjusted to 8. The aqueous phase was extracted with chloroform (3×), and the combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 60 mg of an oil which solidified on standing. This was shown to be a mixture of IIa and IIb by tlc.

Separation was effected on silica gel (0.5-mm plate thickness) using ethyl acetate:ethanol:ammonia (90:10:3) as the solvent system (freshly prepared). About 10 mg was applied to each plate. After elution about 50 mg of IIa and 6 mg of IIb were isolated. Both compounds solidified on standing or could be precipitated from ether:petroleum ether, mp IIb = 85–88°. IIa: ir (KBr) λ_{max} 3400 (broad), 2960, 1640, 1505, 1465, 1325, 1120, 1050, 980, 915 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.3 (m, 4 H, on addition of D_2O one peak disappears), 4.62 (d, J = 4, 1 H), 4.2–4.4 (broad, 1 H). IIb: ir (KBr) λ_{max} 3400 (broad), 2955, 1625, 1505, 1450, 1370, 1325, 1120, 1055, 985, 920 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.3 (m, 4 H, on addition of D_2O one peak disappears), 4.52 (d, J = 6, 1 H), 3.3–3.6 (broad, 1 H).

3,6,14-Tritosylate of 6-Hydroxy Derivatives IIa and IIb (III). The mixture (70 mg; 0.2 mmol) obtained from sodium borohydride reduction of naloxone was dissolved in pyridine (3 ml) and *p*-toluenesulfonyl chloride (172 mg; 0.9 mmol) was added. The solution was allowed to stand at room temperature overnight, after which time the pyridine was evaporated *in vacuo*. The residue was dissolved in chloroform and extracted with an aqueous solution at pH 8. The organic phase was dried, filtered, and evaporated *in vacuo* to give about 170 mg of oily III, which did not solidify: ir (KBr) λ_{max} 2960, 1600, 1490, 1415, 1375, 1195, 1180, 820, 660, 575, 555 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.5 and 7.6–8.0 (m, 12 H), 6.3–6.7 (m, 2 H), 4.8–5.6 (m, 3 H), 4.43 (d, J = 4, 1 H), 2.48 (broad singlet, 9 H, on expanded scale this peak is comprised of three sharp peaks).

Reaction of Tosylate III with Tetrabutylammonium Acetate. Compound III (144 mg, 0.3 mmol) was dissolved in *N*-methylpyrollidone (3 ml) and then tetrabutylammonium acetate (120 mg; 0.4 mmol) was added. The reaction was heated at 140° for 3 hr, after which period the cooled reaction was diluted with a saturated sodium chloride solution, and extracted with chloroform (2×). The organic extracts were dried, filtered, and evaporated *in vacuo*. Since all of the solvent was not removed by evaporation the residue was passed through a dry column of silica gel (about 20 gm). The silica gel was deactivated as described by Loev.[17] The solvent system was ethyl acetate:ethanol (9:1). The desired product was collected in the first few fractions, while the *N*-methylpyrollidone remained on the column. The tosylate obtained was dissolved in 5% potassium hydroxide in ethanol (20 ml) and heated under reflux for 2 hr. The reaction was diluted with water and acidified. The aqueous phase was extracted with chloroform, which was discarded. The pH of the aqueous phase was then adjusted to 8 and then was extracted with chloroform:2-propanol (3:1). The combined organic extracts were dried, filtered, and evaporated *in vacuo*. The oil obtained was purified by preparative tlc as described above to isolate 12 mg of IIb, which was identical with IIb isolated directly from the sodium borohydride reduction of naloxone (*via* tlc and ir).

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine 3,6-Diacetate (IVa).** Compound IIa (9 mg) was dissolved in pyridine (1 ml) and 2 drops of acetic anhydride were added. The solution was allowed to stand overnight at room temperature after which time it was evaporated *in vacuo*. Thin-layer chromatography of the oil obtained showed only one compound present. The oil could not be induced to solidify. The ir spectrum (KBr) showed two carbonyl absorptions (1770 and 1740 cm^{-1}) corresponding to the 3- and 6-acetates, respectively; nmr ($CDCl_3$) δ 6.6–6.9 (2 H, arom), 4.9–5.7 (m, 3 H), 4.75 (1 H, corresponds to H^5), 4.32 (1 H, corresponds to H^6), 2.28 (s, 3 H), 1.80 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine 3,6-Diacetate (IVb).** Acetylation of IIb (9 mg), as described above for IIa, gave an oil after evaporation of the solvent. An ir spectrum showed two peaks corresponding to the acetate absorptions; nmr ($CDCl_3$) δ 6.6–6.9 (2 H, arom), 4.9–5.8 (m, 3 H), 4.68 (1 H, corresponds to H^5), 3.3–3.6 (corresponds to H^6, upfield portion is superimposed on other methylene absorptions), 2.26 (s, 3 H), 2.08 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine 3,6,14-Triacetate (IVc).** Diacetate IVa (10 mg) was dissolved in a minimum amount of acetic anhydride and heated on a steam bath for 15 min. The solvent was removed *in vacuo* to give IVc as an oil. An ir spectrum showed bands at 1770 cm^{-1} (3-acetate) and a broad band at 1740 cm^{-1} (6- and 14-acetates); nmr ($CDCl_3$) δ 6.6–6.8 (2 H, arom), 4.9–5.7 (m, 3 H), 4.5–4.8 (m, 2 H, corresponds to H^5 and H^6), 4.35 (d, J = 6, 1 H), 2.26 (s, 3 H), 2.13 (s, 3 H, corresponds to 14 OAc methyl), 1.80 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine 3,6,14-Triacetate (IVd).** Acetylation of IVb (10 mg) was carried out as described above for IVc. An ir spectrum showed carbonyl peaks corresponding to the three acetate groups; nmr ($CDCl_3$) δ 6.6–6.8 (2 H arom), 4.9–5.7 (m, 3 H), 4.63 (1 H, corresponds to H^5), 4.35 (d, J = 6, 1 H), 3.3–3.6 (corresponds to H^6, upfield portion is superimposed on other methylene absorptions), 2.26 (s, 3 H), 2.23 (s, 3 H), 2.08 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine (Va).** Naloxone (150 mg; 0.45 mmol) was dissolved in anhydrous diethyl ether (30 ml) in a three-neck 100-ml round-bottom flask equipped with a condenser and a rubber septum. The flask was cooled in ice and a positive pressure of nitrogen was maintained while methyllithium (3 ml, 1.85 *M* solution) was added *via* a syringe through the septum. The milky white reaction mixture was allowed to stir for 18 hr at room temperature after which time the pH was adjusted to 8 with a saturated ammonium chloride solution. The ether phase was separated, and the aqueous phase was extracted with chloroform (2×). The combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 144 mg of a mixture of naloxone and Va. 6-Methyl derivative Va was isolated by preparative tlc on silica gel (0.5 mm thickness) using ethyl acetate:ethanol:ammonia (90:10:3) as the solvent system. Compound Va (50 mg) was eluted with chloroform:methanol. It is a low melting amorphous solid that precipitated from ether:petroleum ether.

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 14-Acetate (Vb).** The 3,14-diacetate of naloxone[15] was reacted as described for naloxone. Diacetate (137 mg) yielded 125 mg of a mixture consisting of naloxone, Va, and Vb. Using the chromatographic procedure employed above, 15 mg of Vb was isolated as an oil which could not be induced to solidify.

Isolation of 6-Methyl Epimers Va and VIa. Naloxone (3.014 g, 9.2 mmol) was dissolved in anhydrous dioxane (200 ml) and reacted with methyllithium (10 ml, 2.2 *M* CH_3Li) in a manner analogous to that described above. Three grams were isolated after neutralization and extraction. The product was purified by dry column chromatography using silica gel that was suitably treated.[17] A loading ratio of 600:1 was used with a column 2 ft × 1.75 in. The solvent employed was ethyl acetate:ethanol:ammonia (90:10:2). The less polar naloxone was collected prior to a mixture of Va

and VIa (1.5 g). The mixture obtained in this manner was further purified by dry column chromatography using a loading ratio of 100:1. The column was run, using 500-mg samples of the mixture. A portion of compounds VIa and Va isolated by the above technique was then purified by tlc on silica gel (0.5-mm plate thickness) to obtain samples for spectra. Both epimers were amorphous solids that precipitated from ether:petroleum ether: mp Va 101–104° and VIa 92–96°. Va: ir (KBr) λ_{max} 3350 (broad), 1640, 1620, 1505, 1460, 1165, 1100, 950, 905, 790 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.32 (s, 1 H), 1.27 (s, 3 H). VIa: ir (KBr) λ_{max} 3400 (broad), 1645, 1620, 1505, 1460, 1149, 1097, 940, 802 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.36 (s, 1 H), 1.38 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3-Acetate (VIb).** Compound VIa (8 mg, 0.023 mmol) was dissolved in pyridine (1 ml) and acetic anhydride (4 μl, 0.04 mmol) was added. The solution was allowed to stand overnight at room temperature after which time the solvent was evaporated *in vacuo*. Thin-layer chromatography showed only one compound present in the residue. An ir spectrum (KBr) of the oil showed an absorption at 1770 cm^{-1} corresponding to the 3-acetate group; nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 5.9 (broad, 1 H, disappears on addition of D_2O), 5.0–5.6 (m, 3 H), 4.34 (s, 1 H), 2.29 (s, 3 H), 1.23 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 3-Acetate (Vc).** Acetylation of Va (25 mg) was carried out as for VIb. An ir spectrum of the oil obtained verified the presence of the 3-OAc (1775 cm^{-1}); nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 4.9–5.4 (m, 3 H), 4.35 (s, 1 H), 3.88 (broad, disappears on addition of D_2O) 3.39 (broad, disappears on addition of D_2O), 2.31 (s, 3 H), 1.30 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3,14-Diacetate (VIc).** Compound VIa (14 mg) was dissolved in a minimum amount of acetic anhydride and heated under reflux for 30 min. The solvent was removed *in vacuo* to give 15 mg of VIc as an oil. An ir spectrum (KBr) showed peaks at 1770 and 1735 cm^{-1} corresponding to the 3- and 14-acetate groups, respectively; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, one peak disappears on addition of D_2O), 4.38 (s, 1 H), 4.35 (H^9, superimposed on H^5), 2.31 (s, 3 H), 2.15 (s, 3 H), 1.21 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 14-Acetate (Vb).** Compound Va, isolated from the reaction of naloxone 3,14-diacetate with methyllithium, was purified by tlc on silica gel using the system previously described to give Vb. An ir spectrum (KBr) contained a carbonyl absorption at 1745 cm^{-1}. The oil could not be induced to crystallize; nmr ($CDCl_3$) δ 6.4–6.6 (2 H, arom), 4.9–5.6 (m, allyl group), 4.34 (s, 1 H), 4.18 (d, J = 6, 1 H), 2.06 (s, 3 H), 1.30 (s, 3 H).

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Registry No.—IIa, 20410-95-1; IIb, 53154-12-4; III, 53154-13-5; IVa, 53154-14-6; IVb, 53154-15-7; IVc, 53154-16-8; IVd, 53154-17-9; Va, 53154-18-0; Vb, 53154-19-1; Vc, 53154-20-4; VIa, 53154-21-5; VIb, 53154-22-6; VIc, 53154-23-7; *p*-toluenesulfonyl chloride, 98-59-9; naloxone, 465-65-6; naloxone 3,14-diacetate, 50510-01-5.

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Stereochemistry of Nucleophilic Addition Reactions. The Addition of Diethyl Malonate to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. Equilibration of 1-*tert*-Butyl-3-carboxymethylcyclohexane-4-carboxylic Acids

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The Michael addition of diethyl malonate to ethyl 4-*tert*-butylcyclohexene-1-carboxylate gives three of the four possible malonate adducts and the corresponding acetates. The effect of solvent upon the stereochemistry of the addition has been investigated. Under conditions of kinetic control the main product is the *r*-1,*c*-3,*c*-4 isomer (**10**) while under thermodynamic control conditions the *r*-1,*c*-3,*t*-4 isomer predominates. No product of abnormal addition is observed. Equilibration of these adducts with base proceeds mainly by reversal and re-addition. The regioselectivity of the protonation of the intermediate anion is discussed in terms of current theories and the results reconcile the various theories. The equilibrations of the dicarboxylic acids **14**, **15**, **16** and **20** have been studied. $\Delta G°$ for **15** ⇌ **16** is smaller than expected, and for **14** ⇌ **20** less of the diaxial epimer is formed than would be predicted on the basis of $\Delta G°(CO_2H)$. Possible explanations are proposed for these observations.

The stereochemistry of some nucleophilic additions to activated olefins of rigid conformation has been reported. Under conditions of kinetic control, the diethyl malonate anion in ethanol solution adds to 4-*tert*-butyl-1-cyanocyclohexene (**1**) to give the addition product with the malonate group equatorial and the cyanide group axial as the