

ALLYLBORATION OF ISATIN AND 2,3-DIOXOPYRROLO[2,1-*a*]ISOQUINOLINES

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*The reaction of triallylboron with isatin and derivatives 2,3-dioxopyrrolo[2,1-*a*]isoquinolines at room temperature proceeds regiospecifically at the ketone group to give the corresponding homoallyl alcohol. One of these, which contains a lactam and an amide in its structure, was reduced with lithium tetrahydroaluminate to a diamine.*

2,3-Dioxopyrrolo[2,1-*a*]isoquinolines, which have been prepared and studied previously, are of interest as synthons and biologically active compounds [1-8]. Allylborons, unlike other classes of organic derivatives of boron, are known to add to organic compounds with the multiple bonds C=O, C=S, C=N, C=C, and C \equiv C. In all cases allylboronation is accompanied by rearrangement via six-centered transition state with cyclic electron transfer [9-13]. Allylboronation of aldehydes and ketones, discovered in 1964 [13], occurs under mild conditions (-100 to 20°C) and is usually not complicated by side reactions. The reaction may be carried out in any inert solvent (hydrocarbons, CCl_4 , CHCl_3 , etc.) which is one of the virtues of the method.

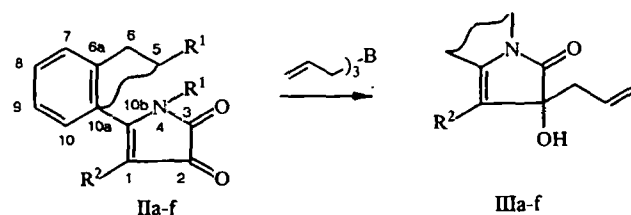
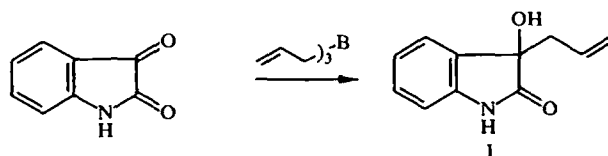
We have found that isatin, on treatment with triallylboron at 20°C , underwent monoallylboronation at the keto group to give the homoallyl alcohol I after deboration with sodium carbonate solution. The tricyclic compounds IIa-f [1-8] react analogously with triallylboron to give the unsaturated alcohols IIIa-f. Dioxopyrroline IV [14, 15], which has a skeleton analogous to the azasteroids, also reacts with triallylboron at the ketone group to give the carbinol V. The polyfunctional ester VII, synthesized by reaction of enamine VI [16] with oxalyl chloride, gave ester VIII analogously. All of these reactions occurred at 20°C in 10-15 min as indicated by decolorization of the intensely red color [4] of solutions of the dicarbonyl starting materials. Two allyl groups of the triallylboron molecule participate in the reaction so the initial pyrroldione and the triallylboron are used in a 2:1 ratio. Amide and lactam functions and the ethoxycarbonyl group (compounds IIc and VII) do not react with the triallylboron. Michael type addition [17] at the enamide double bond of the five-membered ring (compounds II, IV and VII) was also not observed.

The homoallyl alcohols III, V, and VIII have other functional groups which can undergo various reactions. For example, both amide groups in the amide IIIe were reduced with LiAlH_4 to give the aminoalcohol IX, stabilized by a N...HO hydrogen bond. The analogous derivatives of indole lose water and undergo aromatization of the five-membered ring when hydrogenated with LiAlH_4 [18, 19]. That this reaction was not observed in the case cited may be explained by the more complex structure of the molecules and the stability of the H-chelated forms IX. We attempted without success to dehydrate the butenyl alcohols I and III to the corresponding 1,3-dienes.

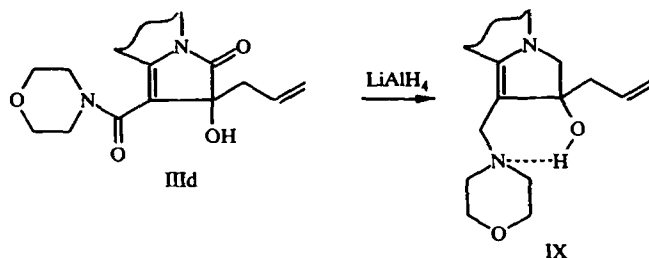
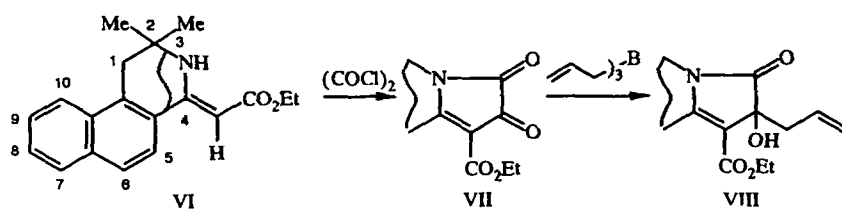
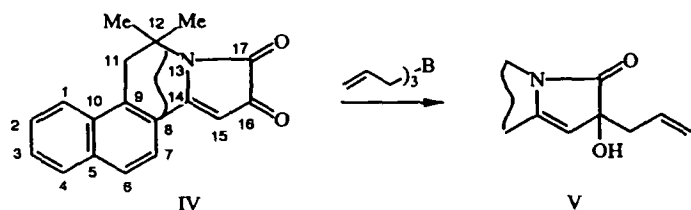
The characteristics of the compounds synthesized are cited in Table 1. The aminoalcohol IX was characterized as its dipicrate. The IR spectra of all the homoallyl alcohols (Table 2) contain absorption bands of the allyl double bond at 1645 cm^{-1} , the lactam carbonyl at $1695\text{-}1710\text{ cm}^{-1}$, the alcoholic hydroxyl group at $3180\text{-}3520\text{ cm}^{-1}$, and also of the corresponding functional groups of the side chains.

In the ^1H NMR spectra (Table 2) of the new homoallyl alcohols the nature and degree of broadening of the signals is very sensitive to the nature of the solvent (CDCl_3 or $\text{DMSO-}D_6$) which may be explained by the presence of several polar groups in the molecules. Two singlets for the methyl groups in position 5 (12) were observed in the spectra of alcohols IIIa, c-f, V, and VIII in contrast to the spectra of the corresponding dicarbonyl compounds. In addition, broadening of the signal of the methylene protons in position 6 was also observed. The AB systems are complicated by the multiplet of the CH_2 protons

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II, III a $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; b $\text{R}^1\text{--R}^1 = (\text{CH}_2)_4$, $\text{R}^2 = \text{H}$;
 c $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CO}[\text{N}(\text{CH}_2)_3]$; d $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{CO}[\text{N}(\text{CH}_2)_4]$;
 e $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CO}[\text{N}(\text{CH}_2)_4\text{O}]$; f $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{COOEt}$



of the allyl group, as a result of which the value of $^2J_{\text{AB}}$ could not be determined. In the spectra of the naphthalene derivatives V and VIII the protons of the CH_2 group at position 11 gave signals at weaker field and consequently the pattern of the AB systems became clearer (Table 2). Thus, the two named methyl groups and the protons of the methylene groups are diastereotopic in consequence of the chiral center at position 2 (16). The position of the signal of the alcoholic hydroxyl depends on the nature of the solvent. For example, in the spectrum of compound IIIb this signal was observed at 5.55 ppm in DMSO-D_6 and at 4.10 ppm in CDCl_3 .

The ^1H NMR spectra of amides IIIc-f (Table 2) are markedly different from both the corresponding initial pyrrolidones and the alcohols IIIa, b, f, V, and VIII. Signals in the spectra of amides IIIc-e are broadened, especially for the CH_3 groups and 6-CH_2 . This phenomenon is evidently due to H-chelation at the amide carbonyl which is absent from the structures of all the other compounds:

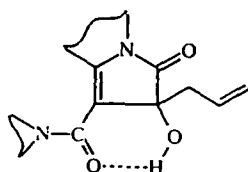


TABLE 1. Characteristics of the Compounds Synthesized

Compound	Molecular formula	(Found, %) (Calculated, %)			mp, °C	Yield, %
		C	H	N		
I	C ₁₁ H ₁₁ NO ₂	<u>69,7</u> 69,8	<u>5,8</u> 5,9	<u>7,5</u> 7,4	123...124	67
IIIa	C ₁₇ H ₁₉ NO ₂	<u>75,6</u> 75,8	<u>7,0</u> 7,1	<u>5,3</u> 5,2	129...130	62
IIIb	C ₁₉ H ₂₁ NO ₂	<u>77,2</u> 77,3	<u>7,1</u> 7,2	<u>4,8</u> 4,7	107...108	63
IIIc	C ₂₃ H ₂₈ N ₂ O ₃	<u>72,5</u> 72,6	<u>7,4</u> 7,4	<u>7,3</u> 7,4	147...148	86
IIId	C ₂₂ H ₂₆ N ₂ O ₃	<u>72,0</u> 72,1	<u>7,1</u> 7,2	<u>7,6</u> 7,6	122...123	53
IIIe	C ₂₂ H ₂₆ N ₂ O ₄	<u>69,1</u> 69,1	<u>6,7</u> 6,9	<u>7,4</u> 7,3	133...134	82
IIIf	C ₂₀ H ₂₃ NO ₄	<u>70,2</u> 70,4	<u>6,6</u> 6,8	<u>4,2</u> 4,1	103...104	57
V	C ₂₁ H ₂₁ NO ₂	<u>78,8</u> 79,0	<u>6,4</u> 6,6	<u>4,5</u> 4,4	153...154	61
VII	C ₂₁ H ₁₉ NO ₄	<u>72,1</u> 72,2	<u>5,4</u> 5,5	<u>4,1</u> 4,0	165...166	70
VIII	C ₂₄ H ₂₅ NO ₄	<u>73,5</u> 73,6	<u>6,3</u> 6,4	<u>3,4</u> 3,6	132...133	58
IX	C ₂₂ H ₃₀ N ₂ O ₂ · 2C ₆ H ₃ N ₃ O ₇	<u>50,0</u> 50,2	<u>4,4</u> 4,5	<u>13,9</u> 13,8	198...199	32

Such an interaction leads to additional restriction of rotation in the amide group [20]. The presence of the H-chelate ring in solutions of these amides is confirmed by their IR spectra: they contain broad bands of associated amides at 1610-1620 cm⁻¹ and of hydroxyl groups at 3330-3340 cm⁻¹ (Table 2).

New multiplets for the methylene protons are observed in the ¹H NMR spectrum of compound IX, in contrast to the spectrum of the starting material IIIe. The observation that the OH signal for this compound appears at a relatively weak field (5.30 ppm) and the presence of a broad low frequency band at 3180 cm⁻¹ in the IR spectrum indicates an H...N(morpholine) intramolecular interaction.

The assignment of the ¹³C NMR signals (Table 3) is based on data presented in a review [17]. It is especially noteworthy that the lowest electron densities and the greatest chemical shifts in the pyrrolidione starting materials and the corresponding alcohols occur at position 5 of the pyrrolidiones, i.e., in position 10b (14). These assignments were also taken into account for the ¹³C NMR spectra of dioxypyrroline starting materials. The spectra of the alcohols synthesized contain signals for carbon atoms in position 1 (15) (101.0-110.0 ppm), the lactam carbon (139.0-149.8 and 175.5 ppm in lactam I), and atom 10b (176.4-180.0 ppm) [17]. The signals of the starting materials, e.g., lactam VII are found in approximately the same fields. The observation that the signal of the ketone carbonyl is absent from the spectra of the alcohols, while the signal of atom 10b (14) remains indicated that atom 10b is not affected by allylboronation, i.e., that the reaction occurs at the ketone carbonyl. A new carbon signal appears in the 77.9-79.4 ppm region which corresponds to the alcohol unit.

The ¹³C NMR spectrum of compound IX, a tertiary enamine, differs markedly from that of the initial amide. Reduction of the two carbonyl groups and the presence of conjugation in the N-C=C unit causes a sharp shift of the signal of C₍₁₎, C₍₂₎ and C_(10b) to stronger field (Table 3).

EXPERIMENTAL

IR spectra of CHCl₃ solutions (0.01 mol/liter) were recorded with a Perkin-Elmer 577 spectrophotometer. The spectrum of the basic alcohol I was recorded in a KBr disk. ¹H and ¹³C NMR spectra were recorded with Bruker AC-200P instrument in DMSO-D₆ (compounds I and IIIb) or CDCl₃ (all the rest).

Compounds were recrystallized from petroleum ether (70-100°C) (IIIa, b, d, f), methanol (picrate of compound IX), or benzene (the rest).

All operations with organoboron compounds were carried out in an atmosphere of dry argon.

The syntheses of the dioxypyrroline starting materials are described in [1-3] and that of compound VI in [16].

TABLE 2. ^1H NMR and IR Spectra of the Compounds Synthesized

Compound	^1H NMR spectrum, δ , ppm						IR spectrum, ν , cm^{-1}				
	1(15)-H, s	5(12)-(CH ₂) ₂ s	$\frac{6(11)\text{-CH}_2}{\text{CH}_2\text{-C}^*}$, m	$\frac{\text{CH}_2\text{-CH}}{\text{both m}}$	aromatic protons, m	OH, s	other protons	C=C (allyl)	lactam C=O	side chain C=O	other bands
I	—	—	2,50	4,88; 5,40	6,70...7,45 (4H)	3,60	6,05 (NH)	1645	1710	—	3205 (NH) 3305 (OH)
IIIa	5,75	1,43; 1,61	2,50...2,90	5,20; 5,77	7,18...7,65 (4H)	3,37	—	1645	1710	—	3380 (OH)
IIIb	5,90	—	2,20...2,65	5,0; 5,90	7,20...7,40 (3H); 7,75 (10-H)	5,55	1,49...2,0 m 8H, 5-(CH ₂) ₄	1645	1705	—	3390(OH)
IIIc	—	•	2,50...3,15	5,10; 5,70	7,10...7,65 (4H)	a ²	3,15...4,27 m (4H, 2CH ₂ N); 1,0...2,0 m (12H, 3CH ₃ and 2CH ₃)	1645	1710	1610	3330 (OH)
IIId	—	•	2,50...3,0	5,07; 5,77	7,15...7,67 (4H)	a ²	1,0...2,0 m (10H, 2CH ₂ and 2CH ₃); 3,50 m (4H, 2CH ₂ N)	1645	1705	1620	3340(OH)
IIIe	—	1,20; 1,65	2,50...3,05	5,10; 5,40	7,10...7,70 (4H)	a ²	3,05...4,15 m (8H, N(CH ₂) ₂ and O(CH ₂) ₂)	1645	1710	1620	3340(OH)
IIIf	—	1,42;1,50	2,70...3,0	5,08; 5,54	7,43...7,50 (3H) 8,15 (10-H)	3,40	1,35 t (3H, CH ₃ CH ₂); 4,35 q (2H, CH ₃ CH ₂)	1645	1695	1720	3520(OH)
V	5,87	1,50; 1,75	a ³	5,15; 5,80	7,26...8,08 (6H)	2,90	—	1645	1710	—	3370(OH)
VII	—	1,57	3,37 s	—	7,57...8,20 (6H)	—	1,35 t (3H, CH ₃ CH ₂); 4,36 q (2H, CH ₃ CH ₂)	—	1700	1730	1745(C=O)
VIII	—	1,50; 1,56	a ³	5,10; 5,60	7,50...8,12 (6H)	3,70	1,35 t (3H, CH ₃ CH ₂); 4,35 q (2H, CH ₃ CH ₂)	1645	1700	1720	3510(OH)
IX	—	1,07; 1,31	a ⁴	5,0; 5,70	7,0...7,45 (4H)	5,30	2,18...3,25 m, 8H; N(CH ₂) ₃ and 6-CH ₂ ; 3,63 s (2H, CH ₂ N)	1645	—	—	3180(OH)

*Hidden by the multiplet at 1.0-2.0 ppm.

*²Hidden by the 6(11)-CH₂ and H₂C-C= multiplets.*³V: 11-C: CH_AH_B - $\delta_A = 3.10$, $\delta_B = 3.22$, $^2J_{AB} = 16.1$ Hz; 2.60 m (CH₂C=C). VII: 11-C: CH_AH_B $\delta_A = 3.18$, $\delta_B = 3.30$, $^2J_{AB} = 16.0$ Hz; 2.90 m (CH₂C=C).*⁴Hidden by the multiplet at 2.18-3.25 ppm.

TABLE 3. ¹³C NMR Spectra of the Compounds Synthesized, δ, ppm

Compound	C ₍₁₎ [C ₍₁₅₎]	C ₍₂₎ [C ₍₁₆₎]	C ₍₃₎ [C ₍₁₇₎]	C ₍₅₎ [C ₍₁₂₎]	C ₍₆₎ [C ₍₁₁₎] CH ₂ C-CH ₂ N	R ¹ , CH ₂ C	H ₂ C- -HC-	Ar	C _(10a) [C ₍₁₄₎]	Other signals
I	—	179.0	75.5	—	42.2	—	109.6; 131.8	131.6; 141.7 (C _(3a) , C _(7a)); 119.0; 121.7; 124.3; 129.0	—	—
IIa	103.0	77.9	141.0	53.5	42.6; 44.3	25.6; 27.0 (Me)	119.3; 133.0	125.6 (C _(3a)); 131.6 (C _(10a)); 124.4; 126.9; 128.5; 129.5	180.0	—
IIb	103.3	78.2	141.4	63.8	42.4; 42.6	25.2; 25.3 (2CH ₂); 3.70; 37.1 (2CH ₂)	119.0; 133.8	124.3 (C _(3a)); 131.6 (C _(10a)); 124.3; 126.8; 128.3; 129.2	179.3	—
IIc	107.4	78.9	139.0	53.5	41.6; 42.3; 44.7; 47.5	24.1; 25.1 (2Me); 25.6; 27.4 (3CH ₂)	118.8; 134.9	125.2 (C _(3a)); 130.7 (C _(10a)); 126.2; 127.0; 128.6; 131.4	176.4	166.0, C(O)N-
IIId	107.0	79.2	139.4	53.5	42.0; 44.6; 45.4; 47.2	24.0; 25.3 (2Me); 26.8 (2CH ₂)	118.4; 134.5	125.4 (C _(3a)); 130.6 (C _(10a)); 125.9; 127.1; 128.6; 131.8	176.5	165.5, C(O)N-
IIIf	110.0	79.4	139.5	53.8	41.8; 44.5; 46.6	25.0; 26.3 (2Me)	119.0; 134.4	126.3 (C _(3a)); 130.5 (C _(10a)); 124.8; 127.0; 128.7; 131.3	176.9	165.4, C(O)N-; 66.1, (CH ₂) ₂ O
IIIf	106.4	78.14	149.8	54.3	42.7; 45.0	25.5; 26.3 (2Me); 14.2 (CH ₃ CH ₂)	119.5; 136.1	124.6 (C _(3a)); 130.7 (C _(10a)); 126.4; 128.1; 130.8; 132.0	176.4	60.3 (CH ₂ O); 164.0 (CO ₂ Et)
V	104.3	78.0	141.2	53.1	39.6; 42.6	26.0; 27.4 (2Me)	119.3; 133.8	122.7 (C ₍₉₎); 126.8; 129.2; 131.3 (C ₍₁₀₎ , C ₍₅₎ , C ₍₈₎); 121.4; 123.4; 126.8; 127.2; 128.7; 131.6	180.0	—
VII	101.0	166.9	157.3	53.2	39.1	25.8 (2Me); 13.9 (CH ₃ CH ₂)	—	120.0 (C ₍₉₎); 130.4; 136.1; 137.5 (C ₍₁₀₎ , C ₍₅₎ , C ₍₈₎); 124.9; 125.6; 126.8; 127.5; 128.7; 129.7	178.4	60.8 (CH ₂ O); 162.6 (CO ₂ Et); 166.9 (C ₍₁₆₎)
VIII	106.9	78.3	149.4	53.6	39.8; 42.5	25.7; 26.3 (2Me); 14.1 (CH ₃ CH ₂)	119.5; 134.7	122.0 (C ₍₉₎); 128.5; 130.6; 134.0 (C ₍₁₀₎ , C ₍₅₎ , C ₍₈₎); 123.9; 125.9; 126.2; 126.7; 127.7; 130.7	176.2	60.2 (CH ₂ O); 164.0 (CO ₂ Et)
IX	65.8	29.6	*	56.7	31.5; 34.1; 52.0; 53.5; 53.8 (4CH ₂ N)	26.3; 28.4 (2Me)	116.0; 134.8	132.9, 134.1 (C _(3a) , C _(10a)); 125.6 (8,9-C); 126.1, 129.5 (C ₍₇₎ , C ₍₁₀₎)	136.9	67.1, O(CH ₂) ₂

*Signal of one of the NCH₂ groups.

3-Allyl-3-oxyindolone-2 (I), 2-Allyl-2-oxy-3-oxo-5,5-(R¹)₂-1-R²-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolines (IIIa-f), gona-16-Allyl-16-oxy-17-oxo-12,12-dimethyl-13-aza-1,3,5(10),6,8(9),14-hexaene (V), and gona-16-Allyl-16-oxy-17-oxo-12,12-dimethyl-15-carbethoxy-13-aza-1,3,5(10),6,8(9),14-hexaene (VIII) (General Method). Triallylboron (1.04 ml, 6 mmol) was added dropwise with stirring to a solution of the corresponding dicarbonyl compound (10 mmol) in absolute chloroform (50 ml) at 20°C. The clear red color of the solution was extinguished over 10 min. The solution was stirred at 20°C for a further 20 min and then methanol (0.5 ml) and saturated Na₂CO₃ solution (5 ml) were added in turn. The organic layer was separated, washed with water dried over K₂CO₃, the chloroform evaporated, the solid separated, dried, and recrystallized.

15-Carbethoxy-16,17-dioxo-12,12-dimethyl-13-aza-1,3,5(10),6,8(9),14-hexaene (VII). A mixture of the enamine (VI) (2.66 g, 10 mmol) and triethylamine (2.76 g, 20 mmol) in ether (150 ml) was added at 0-5°C over 15 min to oxalyl chloride (0.86 ml, 10 mmol) in absolute ether (150 ml). The reaction mixture warmed to 20°C and was kept at that temperature for 30 min. The precipitate was filtered off, washed with water, dried, and recrystallized.

1-(N-Morpholinomethyl)-2-allyl-2-oxo-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2.1-*a*]isoquinoline (IX). Lithium tetrahydroaluminate (0.57 g, 15 mmol) was added with stirring to compound IIIe (3.82 g, 10 mmol) in absolute ether (50 ml). The mixture was boiled for 6 h, then cooled to 20°C, diluted with water (10 ml), and the ether layer separated. The Al(OH)₃ was washed with ether (3 × 10 ml). The combined ether extracts were dried over K₂CO₃, the ether evaporated to 20 ml and treated with a solution of picric acid (4.58 g, 20 mmol) in methanol (20 ml) to give the dipicrate IX which was filtered off, dried and recrystallized.

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