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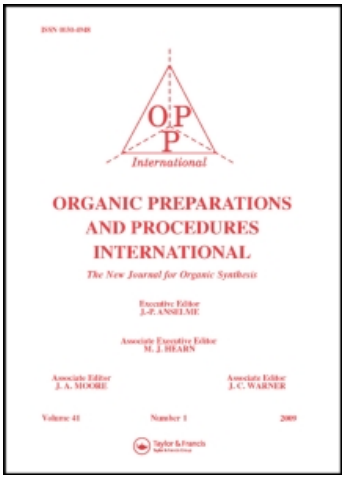

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A MILD METHOD FOR DEHYDRATING SOME CARBINOLS TO ALKENES. 1,1-DIARYLAMINOALKENES AS ANALGESICS

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A MILD METHOD FOR DEHYDRATING SOME CARBINOLS TO ALKENES. 1,1-DIARYLAMINOALKENES AS ANALGESICS†

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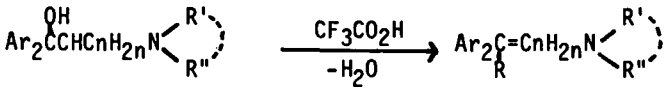
In a continuing search for useful analgesics, certain diphenyl aminocarbinols (I) and diphenyl aminoalkenes (II) [1,2] were found to have mild activity. The alkenes appeared to be best since they had less other CNS activities.[3] Therefore a number of alkene analogs were prepared by dehydration of the carbinols.



I II

Previously described dehydration methods [1,4] worked well if the compounds were stable enough to withstand the relatively harsh procedures; however, when the amino group was azetidine, complex mixtures were obtained containing unreacted carbinol and/or azetidine ring-opened materials. A method [5] using CF_3COOH and $(CF_3CO)_2O$ at reflux was found to give the desired azetidine compound, IIh, but still with some decomposition. Investigation of this procedure showed that CF_3COOH alone at room temperature would completely dehydrate the carbinol in less than one hour without any apparent decomposition. This is doubtless due to the strong acidity and low nucleophilicity of this reagent. Although trifluoroacetic acid is known to be a dehydrating agent its usefullness is apparently not fully appreciated in this type of reaction.

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Subsequently this mild procedure was extended to a number of carbinols of type I and in most cases it gave nearly quantitative yields of the corresponding alkene, II, (Table 1) as shown by TLC and/or NMR. Of the twenty-five compounds tried, all but seven (Table 2) were very successful and this procedure was considered the method of choice. One compound (IIr) with p-Cl group in each benzene ring, required a much longer time, up to 24 hrs. at room temperature, to go to completion. Four carbinols, with F, Cl, Br, or CF_3 in the meta position of each ring, did not dehydrate at all with CF_3COOH alone but were converted cleanly to the alkenes with CF_3COOH and $(CF_3CO)_2O$ at reflux. The carbonol with four CF_3 groups (3,5-Di-CF_3) in each ring) failed under either set of conditions but dehydrated to IIε using concentrated H_2SO_4. The carbinol with p-$(CH_3)_2N$- in each ring seemed to dehydrate to some extent with CF_3COOH but conc H_2SO_4 gave the best yield of IIη. One compound (IIt) with thienyl group instead of phenyl was obtained smoothly from the carbinol with CF_3COOH under the usual conditions.

These alkenes were screened in rats using the "hot plate" method,[6] usually at a dose only up to 12.5 mg/kg. Those showing ED_{50}'s below this dose were: IIc, 5; IIf, 3.5; IIh, 8; IIk, 5.6 and IIβ, 10 mg/kg. Two of the starting carbinols[1] (starting materials for IIh and IIk) were tested and found to be active. β-Methyl-α,α-diphenyl-1-azetidinepropanol hydrobromide had an ED_{50} of 8 and β-methyl-α,α-diphenyl-1-pyrrolidinepropanol hydrochloride had an ED_{50} of 5. Under the conditions of this test morphine sulfate showed ED_{50} 1 mg/kg.

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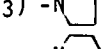
Table 1. $(YC_6H_4)_2C{=}C(R)C_nN_{2n}N\begin{matrix}R'\\R''\end{matrix}\cdot HX$

by Dehydration with CF_3CO_2H (Method A)

No.	Y	R	C_nH_{2n}	$-N\begin{matrix}R'\\R''\end{matrix}$	HX	Crystallization Solvent	Yield % [a]	mp
IIa	H	CH_3	CH_2	NH_2	HCl	EtCOMe	88	221-223[b]
IIb	H	CH_3	CH_2	$-NH(CH_2)_2CH_3$	HBr	Et_2O	52	174-175[c]
IIc	H	CH_3	CH_2	$-N(CH_3)_2$	HCl	EtOAc-Et_2O	96	189-191[d]
IId	H	CH_3	CH_2	$-N(CH_3)CH_2CH_3$	HBr	Et_2O	52	141-145
IIe	H	CH_3	CH_2	$-N(CH_3)CH_2CH{-}CH_2$	HCl	Et_2O	82	158-161
IIf	H	CH_3	CH_2	$-N(CH_2CH{-}CH_2)_2$	HCl	EtOAc-Et_2O	70	143.5-145.5
IIg	H	CH_3	CH_2	$-NHCH_2$- 	CF_3COOH	EtOAc-pet. ether	48	117-120
IIh	H	CH_3	CH_2		base[e]	-	89	53-55
IIi	H	H	CH_2		HCl	MeOH-EtOAc	83	158-161
IIj	H	H	CH_2CH_2		HCl	EtOH-EtOAc	82	161-162
IIk	H	CH_3	CH_2		HCl	EtCOMe		181-183
IIl	H	H	$CH(CH_3)$		HCl	EtOAc	75	135-136.5
IIm	H	CH_3	CH_2		HCl	AcOH-Et_2O	(c)	226.5-229
IIn	H	CH_3	CH_2		HBr	Et_2O	77	203-206
IIo	H	CH_3	CH_2		HBr	Et_2O	50	200-203
IIp	p-CH_3	CH_3	CH_2	$-N(CH_2CH_3)_2$	HCl	EtOH-EtOAc	88	192-193.5
IIq	p-F	CH_3	CH_2		HCl $\cdot H_2O$	EtOAc-Et_2O (dec)	95	122-135[h]
IIr	p-Cl	CH_3	CH_2	$-N(CH_2CH_3)_2$	HCl[i]	EtOAc-Et_2O	95	169-170.5
IIs	p-OCH_3	CH_3	CH_2		HBr	Et_2O	94	238-241
IIt	 S(j)	CH_3	CH_2		HBr	Et_2O	24	134-137

a) The yields are for isolated material melting no less than 2° below the reported mp and having satisfactory (except where indicated) physical specifications.

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b) Reported by B. Blank, W. A. Screicacottoli, J. Med. Chem. 12, 271 (1969), prepared by a different method, mp 233-235°.

c) Melted at 162-165°, resolidified and remelted at 174-175°.

d) Prepared as described by Jones et al, reference (4c).

e) Purified by distillation in a sublimation apparatus at 50-60°/0.001-0.002 mm giving colorless oil which crystallized on rubbing. A hydrochloride salt was also prepared. See Experimental Section.

f) Previously reported in reference (1), prepared using p-TsOH-xylene. The free base was also prepared in quantitative yield by Method A.

g) See reference (1).

h) Karl Fischer analysis showed this to be a mono hydrate. Calcd.: H_2O, 4.67. Found: 4.65.

i) The dehydration was not complete after 2 hr. but was complete after 24 hr. at room temperature.

j) Thienyl instead of Y-C_6H_4

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Table 2. $(YC_6H_4)_2C{=}C(CH_3)CH_2N\langle^{R'}_{R''}$ by Dehydration with CF_3CO_2H-$(CF_3CO)_2O$ (Method B) or H_2SO_4.

No.	Y	-N$\langle^{R'}_{R''}$	HX	Crystallization Solvent	Yield %[a]	mp
IIα	m-F	-N⬡	HBr	Et_2O	68	144-146[b]
IIβ	m-Cl	$N(CH_2CH_3)_2$	HCl	EtCOMe-Et_2O	86	143-144.5
IIγ	m-Br	$N(CH_2CH_3)_2$	HBr	Et_2O	68	161-165
IIδ	m-CF_3	N⬡	CF_3CO_2H	EtOAc-pet.ether	-	141-145[c]
IIε	3,5-diCF_3	N⬡	HBr[d]	Et_2O	74	259-261 (dec)
IIζ	p-OH	N⬡	HCl[d]	EtOH	22	216-217
IIη	p-$N(CH_3)_2$	N⬡	3HBr	EtOAc	84	168-174 (dec)

a) See footnote (a), Table 1.

b) IR and NMR indicated the presence of one-half molecule of water. The compound sintered at 125° before melting at 144-146°.

c) Mp 141-145° after sintering at 137°.

d) See Experimental Section.

e) Carbinol dehydrated in H_2SO_4 solution at room temperature for 15 min.

Table 3. Elemental Analyses for Compounds II

Compound	C Calcd. (Found)	H Calcd. (Found)	N Calcd. (Found)	Halogen Calcd. (Found)
IIa	73.98 (73.83)	6.98 (6.84)	5.39 (5.26)	Cl, 13.65 (13.80)
IIb	65.89 (65.79)	6.99 (7.06)	4.04 (3.92)	Br, 23.08 (23.22)
IId	65.89 (65.98)	6.99 (7.09)	4.04 (4.21)	Br, 23.08 (22.94)
IIe	67.04 (67.23)	6.75 (7.17)	3.91 (3.86)	Br, 22.30 (22.31)
IIf	77.74 (77.51)	7.72 (7.57)	4.12 (4.13)	Cl, 10.43 (10.29)
IIg	67.50 (67.33)	6.18 (6.20)	3.58 (3.52)	F, 14.56 (15.5)
IIh	86.64 (86.62)	8.04 (8.04)	5.32 (5.34)	- -
IIi	76.11 (75.58)	7.40 (7.60)	4.67 (4.67)	Cl, 11.82 (11.70)
IIj	76.53 (75.58)	7.71 (7.64)	4.46 (4.50)	Cl, 11.29 (11.40)
IIl	76.53 (76.29)	7.71 (7.53)	4.46 (4.40)	Cl, 11.29 (11.34)
IIn	68.39 (68.79)	7.30 (7.58)	3.63 (3.39)	Br, 20.68 (20.35)
IIo	64.17 (63.74)	6.46 (6.46)	3.74 (3.76)	Br, 21.35 (21.25)
IIp	76.83 (76.75)	8.79 (8.83)	4.07 (4.13)	Cl, 10.31 (10.25)
IIq	65.30 (65.10)	6.58 (6.56)	3.81 (3.93)	Cl, 9.64 (9.92)
IIr	62.43 (62.22)	6.29 (6.31)	3.64 (3.61)	Cl, 27.64 (27.88)
IIs	63.16 (63.33)	6.75 (6.47)	3.35 (3.17)	Br, 19.10 (18.75)
IIt	51.89 (51.50)	5.44 (5.77)	3.78 (3.67)	Br, 21.58 (21.50)
IIα	59.56 (59.84)	5.75 (5.85)	3.47 (3.50)	Br, 19.81 (20.23)
IIβ	62.43 (62.34)	6.29 (6.14)	3.64 (3.64)	Cl, 27.64 (27.38)
IIγ	46.36 (46.50)	4.67 (4.85)	2.70 (2.53)	Br, 46.27 (45.59)
IIδ	54.65 (55.05)	4.20 (4.30)	2.66 (2.59)	F, 32.42 (30.32)
IIε	45.78 (45.54)	3.20 (3.22)	2.22 (2.12)	Br, 12.68 (12.88)
IIζ	69.45 (69.50)	6.99 (6.94)	4.05 (4.03)	Cl, 10.25 (10.18)
IIη	47.54 (46.01)	5.98 (6.14)	6.93 (6.71)	Br, 39.54 (37.97)

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EXPERIMENTAL

Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. IV, UV, NMR and usually mass spec were determined on the new compounds and were in conformity with the proposed structures.

Method A. 2-Methyl-3,3-diphenyltriallylamine Hydrochloride (IIf). - The free base was liberated from 3.58 g (0.01 mole) of α-[2-(diallylamino)-1-methylbenzhydrol hydrobromide[1] with cold dil NaOH and was extracted with CH_2Cl_2. Washing (H_2O and sat NaCl), filtration, and evaporation gave a light tan oily free base.[7] This was dissolved in 15 ml of CF_3COOH, stirred under N_2 at room temperature for 1 hr. and allowed to stand in the refrigerator overnight. Evaporation below 30° gave an oil which was mixed with cold dil NaOH and extracted with CH_2Cl_2. After washing (H_2O and sat NaCl), drying (Na_2SO_4), filtering and evaporating in vacuo, an oil was obtained. This free base was dissolved in 20 ml of EtOAc and acidified with ethanolic HCl. On rubbing it crystallized. After dilution with ether the hydrochloride was collected, washed (EtOAc and Et_2O) and dried yielding 2.38 g (70%) of white crystals, mp 143.5-145.4°.

β-Methyl-α,α-diphenyl-1-azetidinepropanol. - A 3.63 g (0.01 mole) sample of the hydrobromide salt[1] of this carbinol was converted to the free base with NaOH and extracted with CH_2Cl_2. Washing (H_2O and sat NaCl), drying (Na_2SO_4), filtration and evaporation in vacuo gave 2.8 g (99%) of white crystalline solid, mp 93-94° showing only one spot on TLC (silica gel), 57% EtOAc, 31% isooctane, and 12% AcOH).

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.83; H, 8.65; N, 5.00.

1-(2-Methyl-3,3-diphenylallyl)-azetidine Hydrochloride. - A sample of the free base (IIh) in ether was converted to the hydrochloride with ethanolic

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HCl. Recrystallization from EtOAc-Et_2O gave white crystals which changed form on drying, mp 114-115.5°.

Anal. Calcd. for $C_{19}H_{22}ClN$: C, 76.11; H, 7.40; Cl, 11.82; N, 4.67. Found: C, 76.14; H, 7.70; Cl, 11.80; N, 4.62.

Method B. *3,3-Di(m-chlorophenyl)-N,N-diethyl-2-methylallylamine Hydrochloride (IIβ).* Free base was liberated from 2.5 g (0.0062 mole) of 3,3'-dichloro-α-[2-(diethylamino)-1-methylethyl]-benzhydrol hydrochloride[1] with cold dil NaOH, and extracted with CH_2Cl_2. Washing (H_2O and sat NaCl), drying (Na_2SO_4), filtration, and evaporation *in vacuo* gave oily free base. This was dissolved in 15 ml of CF_3COOH and 5 ml of $(CF_3CO)_2O$, stirred under reflux for 7.5 hr. and allowed to stand at room temperature for 3 days. The solution was treated with decolorizing charcoal, filtered, and evaporated *in vacuo*. The resulting oil was mixed with cold dil NaOH, extracted with CH_2Cl_2, washed (H_2O and sat NaCl), dried (Na_2SO_4), filtered and evaporated *in vacuo* giving a light tan oil. This free base was dissolved in 20 ml of EtCOMe, acidified with ethanolic HCl, concentrated and diluted with ether. This gave 2.05 g (86%) of white crystals, mp 143-144.5° Attempts to prepare this compound by Method A or with HCl in AcOH as the dehydrating agent failed and starting material was recovered.

α,α-Bis(p-fluorophenyl)-β-methyl-1-pyrrolidinepropanol Hydrochloride. - A 0.41 g (0.001 mole) sample of the corresponding hydrobromide salt[1] was converted to the free base with NaOH and extracted with CH_2Cl_2. This was washed (H_2O and sat NaCl), dried (Na_2SO_4), filtered and evaporated *in vacuo* giving gummy free base. A solution of this in EtOAc was acidified with ethanolic HCl and diluted with ether. On rubbing 0.35 g of white crystals were obtained, mp 191-192°.

Anal. Calcd for $C_{20}H_{24}ClF_2NO$: C, 65.30; H, 6.58; Cl, 9.64; N, 3.81. Found: C, 65.56; H, 6.75; Cl, 9.75; N, 3.91.

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1-[2-Methyl-3,3-di(3,5-trifluoromethylphenyl)-allyl]-pyrrolidine Hydrobromide (IIε). - A solution of 1.81 g (0.003 mole) of α,α-bis(α,α,α,α',α',α'-hexafluoro-3,5-xylyl)-β-methyl-1-pyrrolidinepropanol hydrochloride in 25 ml of conc H_2SO_4 was heated on a steam bath for 10 min. After standing at room temperature for 30 min it was poured into ice water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed (H_2O), dried (Na_2SO_4), and evaporated in vacuo. The resulting free base in ether was acidified with ethereal HBr giving 1.4 g (74%) of crystalline solid, mp 259-261° (dec). Attempts to dehydrate the carbonol with CF_3COOH, with or without $(CF_3CO)_2O$, failed.

4,4'-[2-Methyl-3-(1-pyrrolidinyl)-1-propenylidene]bisphenol Hydrochloride (IIζ). - p-(2-Pyranyloxy)-phenylmagnesium bromide was prepared from 9.73 g (0.4 mole) of Mg, 96.4 g (0.4 mole) of p-(2-pyranyloxyphenyl)bromide and 300 ml of THF. After stirring for 0.5 hr., 17.1 g (0.1 mole) of methyl β-(1-pyrrolidinyl)-isobutyrate[8] in 30 ml of THF was slowly added and the mixture was stirred under reflux for 3 hr. After cooling 18 ml (1 mole) of water was slowly added, the mixture was filtered through Supercel, and the solid was well extracted with THF. Evaporation of the THF gave 97 g of yellow oil. This was dissolved in 50 ml of water, 16.7 ml (0.2 mole) of conc HCl and 100 ml of acetone and allowed to stand at room temperature for 12 hr. After filtration, the aqueous solution was washed with ether which was back-extracted with water. The aqueous solution was basified with NaOH, filtered and neutralized with CO_2 giving a brown gum. The aqueous solution was decented and the gum was washed with water, dissolved in EtOH and acidified with ethanolic HCl. Dilution with ether gave a crystalline hydrochloride which was collected and recrystallized from ethanol yielding 7.5 g (22%) of white solid, mp 216-217°. IR, NMR, mass spec and analysis showed this to be the dehydrated product IIζ.

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