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RESEARCHES ON THE CHEMISTRY OF HETEROCYCLIC SYSTEMS

XLI. Acidochrome Condensation of Benzylamides of Diarylglycolic acids*

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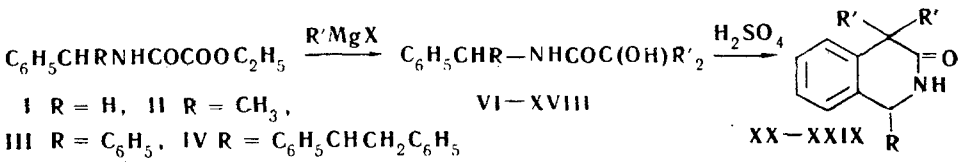
Acidochromic condensation of benzylamides of diarylglycolic acids is used to extend the limits of the method of synthesis of 4,4-diaryl-3-oxo-1,2,3,4-tetrahydroisoquinolines and the effect of side-chain substituents on heterocyclic ring closure is investigated. The starting benzylamides are synthesized by treating esters of benzyloxamic acids with organomagnesium compounds, and acidochrome condensation of the benzylamides is effected by concentrated sulfuric acid. The UV spectra of the benzylamides and their condensation products have spectroscopic characteristics which closely resemble one another.

Acidochromic condensation of arylides of diarylglycolic acids have been studied in relationship to the effect of substituents in the arylide portion [1], in phenyl groups at the carbinol carbon atom [2], or at the nitrogen atom [3,4], on ease of ring closure, and also with regard to the comparative rates of formation of 5-, 6-, 7- and 8-membered rings [5].

The present paper is concerned with the problem of extending a method of synthesizing tetrahydroisoquinoline derivatives [6], and a study of the effects of side-chain substituents on isoquinoline ring closure with benzylamides of diarylglycolic acids. The equations and acidochrome condensation are



I R = H, II R = CH_3, III R = C_6H_5, IV R = $C_6H_5CHCH_2C_6H_5$

VI—XVIII

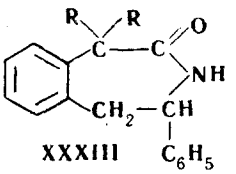
XX—XXIX

The starting esters of benzyloxamic acids I-IV were obtained by reacting the amines with diethyloxalate. Ammonolysis of the ethyl α,β-diphenylethyloxamate (IV) gives the amide V.

The procedure described in [6] was used for carrying out the reaction between esters I—IV and the Grignard compounds. The benzylamides VI-XVIII (Table 1) are crystalline compounds, which exhibit halochromism, the colors given with concentrated sulfuric acid being as follows: benzilic acid derivatives, reddish-brown; 4,4'-dimethylbenzilic and 4,4'-dimethoxybenzilic acid derivatives, crimson; 2,2'-dimethoxybenzilic acid, green; the N-methyl-N-benzylamide of 4,4'-dimethylbenzilic acid (XIX) is very basic, and gives a color with 60% sulfuric acid.

Benzylamides VI-XVIII readily undergo acidochrome condensation when treated with concentrated sulfuric acid, to give 4,4-diaryl-3-oxo-1,2,3,4-tetrahydroquinolines (XX-XXIX) (Table 2); 70-80% sulfuric acid was used to prepare 4,4-di(p-tolyl)-3-oxo-2-methyl-1,2,3,4-tetrahydroquinoline (XXXII).

Starting with the benzylamides XVI, XVII structure, ring closure to a 6-membered tetrahydroquinoline ring, on to a 7-membered benzazepine ring XXXIII can be secured.



XXXIII

However, condensation products XXVIII, XXIX are assigned tetrahydroquinoline derivative structures, because 6-membered ring formation is more rapid than 7-membered ring formation [5].

* For Part XL see [4].

It should be mentioned that there is a considerable rise in melting point on passing from benzylamides (Table 1) to their condensation products (Table 2).

Table 1

Melting Points, Yields, and Analytical Results of Benzylamides of Diarylglycolic Acids

Compound Number	Name	Mp, °C	Formula	N, % Found	N, % Calculated	Yield, %
VI	N-Benzyl benzilamide	97—98	$C_{21}H_{19}O_2N$	4.43 4.49	4.41	86.9
VII	N-Benzyl 4, 4'-dimethyl-benzilamide	108—110	$C_{23}H_{23}O_2N$	4.02 4.10	4.05	93.5
VIII	N-Benzyl 4, 4'-dimethoxy-benzilamide	145—146	$C_{23}H_{23}O_4N$	3.60 3.57	3.71	82.3
IX	N-α-Phenylethyl 2, 2'-dimethoxy-benzilamide	139	$C_{24}H_{25}O_4N$	3.55 3.67	3.58	90.5
X	N-α-Phenylethyl dibenzyl-glycolamide	155	$C_{24}H_{25}O_2N$	4.00 3.94	3.89	69.5
XI	N-Benzohydryl benzil-amide	169—171	$C_{27}H_{23}O_2N$	3.69 3.60	3.56	71.2
XII	N-Benzohydryl 2, 2'-dimethoxy-benzilamide	110—111	$C_{29}H_{27}O_4N$	3.17 3.24	3.09	70.6
XIII	N-Benzohydryl 4, 4'-dimethyl-benzilamide	146—147	$C_{29}H_{27}O_2N$	3.33	3.32	86.9
XIV	N-Benzohydryl 4, 4'-dimethoxy-benzilamide	145—146	$C_{29}H_{27}O_4N$	3.00 3.10	3.09	55.5
XV	N-Benzohydryl dibenzylglycol-amide	209	$C_{29}H_{27}O_2N$	3.44 3.37	3.32	97.8
XVI	α, β-Diphenylethyl benzil-amide	141—144	$C_{28}H_{25}O_2N$	3.58 3.60	3.44	61.4
XVII	α, β-Diphenylethyl 4, 4'-dimethoxy-benzilamide	123—124	$C_{30}H_{29}O_2N$	3.32 3.22	3.22	88.8
XVIII	α, β-Diphenylethyl 2, 2'-dimethoxy-benzilamide	158	$C_{30}H_{29}O_4N$	3.05 2.99	2.99	77.8

Notes. 1) For preparing compounds VI–VIII ethyl benzyloxamate (I) [7] was used, for compounds IX, X ethyl α-phenylethyloxamate (II) [6], for compounds XI–XV ethyl benzohydryloxamate (III) [8], and for compounds XVI–XVIII (IV). 2) Compound VI was recrystallized from toluene, VII from petrol ether, X, XV, from glacial AcOH, and the rest from EtOH.

Investigation of UV absorption spectra* showed the optical properties of the benzylamides and the corresponding tetrahydroisoquinolines to be closely similar, there being a small difference in the degree of absorption (figure).

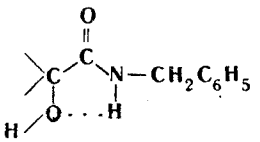
Using the method of [5], the rate of acidochrome condensation was determined for N-benzyl 4, 4'-dimethyl-benzilamides (Table 3).

The results show N and C substituents to have different effects. The former promote and the latter retard cyclization. With increase in the volume of the substituents in VII, XIII, XXXI, and XVII, the rate of cyclization drops (see [10]), while in the case of XVIII, retardation increases so much that generally condensation does not take place. Probably C substituents decrease the number of chain forms which facilitate cyclization.

Apparently the effect of the N-substituents is due to tertiary benzylamides forming, more readily than secondary ones, the amido group cis configuration; in the actual secondary benzylamides hydrogen bonds [11] stabilize the trans

* Measurements were made in EtOH solution, using a SF-4 spectrophotometer.

form of the amido group, XXXIV, which is less favorable for ring formation.



XXXIV

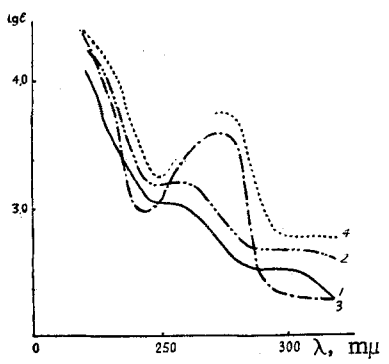
Compounds X and XV do not exhibit halochromism, and do not condense [6], and VIII and XIV do not condense because of the depressed activity of the electrophilic reaction center [5].

Table 2

Melting Points, Yields, and Analytical Data of Tetrahydroisoquinoline Derivatives

Compound number	Name	Mp, °C	Formula	N, % Found	N, % Calculated	Yield, %
XX	4,4-Diphenyl-3-oxo-1,2,3,4-tetrahydroisoquinoline	324	$C_{21}H_{17}NO$	4.77 4.63	4.67	51.8
XXI	4,4-Di(p-tolyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline	223—224	$C_{23}H_{21}NO$	4.12 4.06	4.27	100
XXII	4,4-Di(o-anisyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline	277—277.5	$C_{23}H_{21}NO_3$	3.83 3.87	3.89	70
XXIII	4,4-Di(p-tolyl)-3-oxo-1-methyl-1,2,3,4-tetrahydroisoquinoline	233—235	$C_{24}H_{23}NO$	4.02 4.05	4.10	100
XXIV	4,4-Di(o-anisyl)-3-oxo-1-methyl-1,2,3,4-tetrahydroisoquinoline	284.5	$C_{24}H_{23}NO_3$	3.83	3.75	78.7
XXV	4,4-Diphenyl-3-oxo-1-phenyl-1-2-3-4-tetrahydroisoquinoline	251—253	$C_{27}H_{21}NO$	3.70 3.85	3.73	80.0
XXVI	4,4-Di(p-tolyl)-3-oxo-1-phenyl-1,2,3,4-tetrahydroisoquinoline	203	$C_{29}H_{25}NO$	3.13	3.47	95.7
XXVII	4,4-Di(o-anisyl)-3-oxo-1-phenyl-1,2,3,4-tetrahydroisoquinoline	214	$C_{29}H_{25}NO_3$	3.13	3.21	63.8
XXVIII	4,4-Diphenyl-3-oxo-1-benzyl-1,2,3,4-tetrahydroisoquinoline	225—226	$C_{28}H_{23}NO$	3.65	3.59	99.4
XXIX	4,4-Di-(p-tolyl)-3-oxo-1-benzyl-1,2,3,4-tetrahydroisoquinoline	214	$C_{30}H_{27}NO$	3.43 3.46	3.36	88.8

Notes. 1) For the syntheses of XXII, XXIII N-benzyl 2,2'-dimethoxybenzilamide (XXX) [9] and N-α-phenylethyl 4,4'-dimethylbenzilamide (XXXI) were respectively used [5]. 2) Compounds XX, XXII, XXVII, and XXVIII were recrystallized from glacial AcOH, XXV from toluene, and the rest from EtOH.



UV absorption spectra: 1) VI; 2) XX; 3) XXX, λ_{max} 274 mμ, lg ε 3.64; 4) XXII, λ_{max} 274 mμ, lg ε 3.73.

Experimental

Ethyl α,β-diphenylethyloxamate (IV). 26 g (0.13 mole) α,β-diphenylethylamine and 26 g (0.178 mole) diethyloxalate, were mixed and held at room temperature for 12 hr, then heated until the alkaline reaction vanished. The small amount of solid was filtered off, and the filtrate diluted with 250 ml water. The reaction product which separated was filtered off, and after drying, recrystallized from petrol ether. Plates mp 119°–121° C, yield 25 g (66.7%). Found: N 4.98, 4.84%. Calculated for $C_{18}H_{19}NO_3$: N 4.71%.

α,β-Diphenylethyloxamide (V). Obtained in 87.5% yield by passing NH_3 into an EtOH solution of IV. Needles (ex EtOH), mp 220°–221.5° C. Found: N 10.46, 10.20%. Calculated for $C_{16}H_{16}N_2O_2$: N 10.44%.

N-Benzohydryl benzilamide (XI). PhMgBr was prepared from 15.7 g (0.1 mole) PhBr and 2.4 g (0.1 g at) Mg in 45 ml Et_2O, and 5.66 g (0.02 mole) III

added. The mixture was heated for 1 hr on a water bath, and the Grignard complex then decomposed with dilute HCl. The precipitate was filtered off and recrystallized, yield 5.6 g. Insoluble in water and ether, soluble in other organic solvents.

Table 3

Comparative Rates of Acidochrome Condensation of N-Benzyl 4, 4'-Dimethyl benzilamides

$C_6H_5CHR-NR'-COC(OH)(C_6H_4CH_3\text{-}p)_2$

Compound number	R	R'	Relative rate of condensation*
XIX	H	CH_3	1
VII	H	H	0.34
XXXI	CH_3	H	0.16
XIII	C_6H_5	H	0.10
XVII	$C_6H_5CH_2$	H	0.04

* The following were used in a run: 1 ml 0.15 M solution of amide in glacial AcOH, and 1.5 ml concentrated H_2SO_4; the rate of condensation of XIX, viz., 2'50", was taken as unity.

N-Methyl-N-benzyl-4, 4'-dimethylbenzilamide (XIX). Obtained in 73.5% yield from ethyl N-methyl-N-benzyloxamate and p-tolyl MgBr. Minute crystals (ex petrol ether), mp 100°–101° C. Found: C 80.28, 80.11; H 7.25, 7.07; N 3.96, 3.85%. Calculated for $C_{24}H_{25}NO_2$: C 80.25; H 6.95; N 3.89%.

4, 4-Diphenyl-3-oxo-1-phenyltetrahydroisoquinoline (XXV). 10 ml concentrated H_2SO_4 was added to 3.9 g (0.01 mole) XI dissolved in 15 ml glacial AcOH. The mixture turned brown, and a precipitate formed. 50-ml water was added, the precipitate filtered off, washed with water, then with Na_2CO_3 solution, and finally again with water. Yield 3 g.

4, 4-Di (p-tolyl)-3-oxo-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XXXII). Acidochrome condensation of XIX gave this in 85.2% yield. Plates (ex EtOH), mp 188°–190° C. Found: C 84.41, 84.30; H 6.83, 6.93; N 4.30, N 4.15%. Calculated for $C_{24}H_{23}NO$: C 84.48; H 6.80; N 4.11%.

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