

Reissert Compound Studies. XXVII.
The Reaction of the Anion with 4-Piperidones

Frank D. Popp (1) and Raymond F. Watts

Department of Chemistry, Clarkson College of Technology, Potsdam, N. Y. 13676

Received June 7, 1976

The anion of the isoquinoline Reissert compound has been found to react with 4-piperidones to give esters of tertiary alcohols.

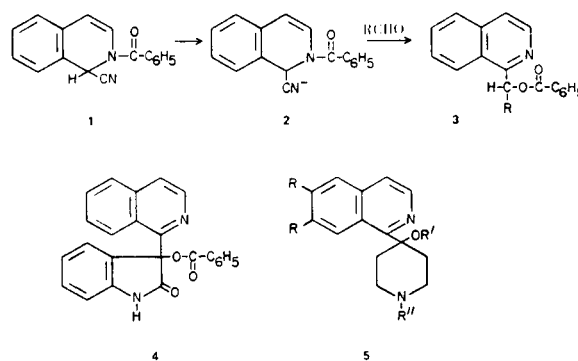
J. Heterocyclic Chem., 13, 1129 (1976).

A number of reports have appeared on the reaction of Reissert compounds with aldehydes (2). Thus the anion (2) of the isoquinoline Reissert compound (1) reacts with aldehydes to give esters (3).

The reaction of 2 with ketones, however, has not met with as much success. McEwen and co-workers (3) were not able to obtain products from acetophenone, propiophenone or benzophenone and 1 using phenyllithium at low temperature. Popp and Wefer (4) did not obtain the desired ester from acetophenone and 1 using sodium hydride in dimethylformamide at room temperature. We (5) have found that the ketone, isatin, reacts to give the expected ester 4. Recently Jończyk (6) has reported the successful reaction of 1 with acetophenone, acetone, and cyclohexenone using an acetonitrile-50% sodium hydroxide system.

We had an interest in compounds of the type 5 in connection with other work in progress in these laboratories and thus investigated the reaction of 2 with 4-piperidones. As indicated in Table I, a variety of 1-substituted-4-piperidones react with 1 using either sodium hydride in dimethylformamide or acetonitrile-50% sodium hydroxide to give esters (5, R' = COC₆H₅). The esters could be easily hydrolyzed to the tertiary alcohol (5, R' = H) and in some cases the crude ester was hydrolyzed directly to the alcohol without characterization of the ester.

Although working in good yield for 4-piperidones this reaction is not as successful with other ketones and the following compounds gave no isolable products using either method: acetylferrocene, 3-acetylindole, adamantyl methyl ketone, estrone-3-methyl ether, 3-ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-one, flavanone, *p*-methoxyacetophenone, 3-quinuclidone hydrochloride, 2,2,6,6-tetramethyl-4-piperidone, thiochroman-4-one, and tropinone.



EXPERIMENTAL (7)

Preparation of Esters.

I. Dimethyl Formamide/Sodium Hydride.

A solution of the Reissert compound (0.01 mole) and the ketone (0.015 mole) in dimethyl formamide (30 ml.) was treated with 50% sodium hydride in oil (0.015 mole) and stirred one hour at room temperature. The mixture was then poured over ice (400 ml.) and the esters isolated by filtration.

II. Acetonitrile/50% Sodium Hydroxide.

A mixture of the Reissert compound (0.01 mole), 50% sodium hydroxide (8 ml.), acetonitrile (5 ml.) and the ketone (0.015 mole) was treated with triethylbenzylammonium chloride (0.05 g.) and stirred one hour at room temperature. The mixture was poured into water (400 ml.) and the products isolated by filtration.

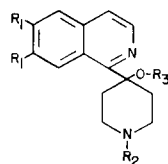
Hydrolysis of the Esters.

A solution of the ester (0.5 g.) in ethanol (25 ml.) and water (25 ml.) was treated with potassium hydroxide (4.0 g.) and refluxed one hour. The ethanol was removed by distillation, the mixture cooled and the alcohol isolated by filtration.

Acknowledgment.

This work was supported in part by a grant from the National Cancer Institute (CA 10965).

Table I



R ₁	R ₂	R ₃	Method (a)	Yield (%)	m.p.	Formula	Analyses		Calcd.
							C	H	Found
H	CH ₃	H	I	83	168-169 (b)	C ₁₅ H ₁₈ N ₂ O	74.40	7.43	11.56
				76			74.32	7.43	11.52
H	CH ₂ CH ₂ C ₆ H ₅	COC ₆ H ₅	I	90	113-115 (c)	C ₂₉ H ₂₈ N ₂ O ₂	79.83	6.42	
							79.81	6.39	
H	CH ₂ CH ₂ C ₆ H ₅	H	I	91	150-151 (d)	C ₂₂ H ₂₄ N ₂ O	79.47	7.18	
							79.47	7.18	
H	CH ₂ C ₆ H ₅	COC ₆ H ₅	I	65	155-157 (e)	C ₂₈ H ₂₆ N ₂ O ₂	79.63	6.16	
							79.82	6.09	
H	CH ₂ CH ₃	COC ₆ H ₅	II	74	130-131 (e)	C ₂₃ H ₂₄ N ₂ O ₂	76.68	6.66	
							76.74	6.68	
OCH ₃	CH ₃	H	II	70	168-170 (f)	C ₁₇ H ₂₂ N ₂ O ₃	67.57	7.28	9.27
							67.63	7.30	9.35
OCH ₃	CH ₂ CH ₂ C ₆ H ₅	COC ₆ H ₅	I	81	179-180 (d)	C ₃₁ H ₃₂ N ₂ O ₄	75.01	6.45	
							75.02	6.42	
H	CH ₃	COCH ₃ (g)	I	70	102-103 (c)	C ₁₇ H ₂₀ N ₂ O ₂			9.85
									9.62
H	CH ₂ C ₆ H ₅ (h)	COC ₆ H ₅	I	55	160-162 (e)	C ₂₈ H ₂₆ N ₂ O ₂			6.63
									6.49

(a) Sodium hydride/DMF-I; methanenitrile/50% sodium hydroxide-II. (b) From benzene/hexane. (c) From petroleum ether. (d) From 2-propanol. (e) From methanol. (f) From chloroform. (g) *N*-Acetyl Reissert compound used. (h) Prepared from 1-benzyl-3-piperidone.

REFERENCES AND NOTES

(1) To whom inquiries should be sent at the Department of Chemistry, University of Missouri-Kansas City, Kansas City, Missouri 64110.

(2) F. D. Popp, *Adv. Heterocyclic Chem.*, **9**, 1 (1968).

(3) L. R. Walters, N. T. Iyer, W. E. McEwen, *J. Am. Chem.* **80**, 1177 (1958).

(4) F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.*, **4**, 183

(1967).

(5) F. D. Popp, C. W. Klinowski, R. Piccirilli, D. H. Purcell, Jr., and R. F. Watts, *ibid.*, **8**, 313 (1971).

(6) A. Jończyk, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **22**, 849 (1974).

(7) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Melting points are taken in capillaries and are uncorrected. All the obtained products gave the expected nmr spectra. Ir spectra were as expected with the C=O absorption of the esters appearing at 1710 cm⁻¹.