Tetrahedron Vol. 36, pp. 3047 to 3051
Pergamon Press Ltd., 1980. Printed in Great Britain

IMINE CHEMISTRY—II†

A NEW ROUTE TO CYCLIC ENAMINONES FROM IMINES AND β-PROPIOLACTONE OR α,β-UNSATURATED ACIDS. THE PREPARATION OF ENAMINO-THIONES

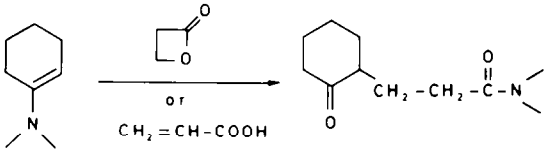
R. SHABANA,* J. B. RASMUSSEN, S. O. OLESEN and S.-O. LAWESSON

Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

(*Received in UK 21 December 1979*)

Abstract— Imines, formed from cyclohexanone and primary aromatic and aliphatic amines, were reacted with β-propiolactone, acrylic, crotonic, and methacrylic acids to give as main products bicyclic lactams, 3,4,5,6,7,8-hexahydro-2-quinolinone, **2**, and enaminones, 2,3,5,6,7,8-hexahydro-4-quinolinone, **3**. The enaminones **3** and a series of noncyclic enaminones **11** were reacted with 2,4-bis (4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, **9**, a new thiation reagent, giving the corresponding enamino-thiones **10** and **12**, respectively. Compound **2a** was also reacted with **9** giving N-phenyl-3,4,5,6,7,8-hexahydro-2-quinolinthione, **13a**. 360 MHz ^{1}H NMR and 90.25 MHz ^{13}C NMR data are reported for the compounds **2a**, **3a** and **10a**.

Enamines, derived from cyclohexanones, undergo smooth reactions with β-propiolactone and α,β-unsaturated acids to give as main products δ-oxocarboxylic amides[1] in reasonable yields:



Scheme 1.

No acylation of the enamines was observed. Also certain enaminones were found to react in the same way to give N-heterocycles.[1] As it is well known that imines are in tautomeric equilibrium with their respective enamines, and thus can react as enamines, we felt prompted to study the reaction of imines with β-propiolactone and α,β-unsaturated acids.

This paper reports a new synthesis of enaminones as well as enamino-thiones. There are known methods, using P_4S_{10},[2-8] for the transformation of enaminones into enamino-thiones, but unfortunately the yields are low. Another method, the reaction of dithiolium salts[2-4] with amines, also gives low to medium yields. However, by using a new thiation reagent, 2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide,-**9**, the enaminones were smoothly transformed into the corresponding vinologous thioamides, enamino-thiones, which are useful for the preparation of thiopyrans[9-11] and thiophenes.[11]

RESULTS AND DISCUSSION

The reaction between imines and β-propiolactone gave as major products enaminones, **3**, but also bicyclic lactams, **2**, were formed. The formation of **2** and **3** can best be rationalized by a pathway involving the enamine, which is known to be in equilibrium with the imine. As β-propiolactone,[13] **4**, can undergo both alkyl-oxygen and acyl-oxygen fissions, the bicyclic lactams, **2**, and enaminones, **3**, can be formed under elimination of water as shown in Scheme 2.

When imines were reacted with acrylic, crotonic, or 2-methacrylic acid, the major products were bicyclic lactams, **2**. A protonation of the imine, which will exist as a "tight ionpair" with the deprotonated acid in low-polar solvents (*i.e.* chlorobenzene), is expected. The "tight ionpair" may collapse giving an activated α,β-unsaturated ester, which can react with another imine in a Michael addition followed by intramolecular acyl-oxygen fission giving bicyclic lactams **2** and enaminones **3**.

The reaction between N-(cyclohexylidine)-aniline, **1a** and β-propiolactone, **4**, or acrylic acid, **5**, gave N-phenyl-3,4,5,6,7,8-hexahydro-2-quinolinone, **2a**, and N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinone, **3a**.

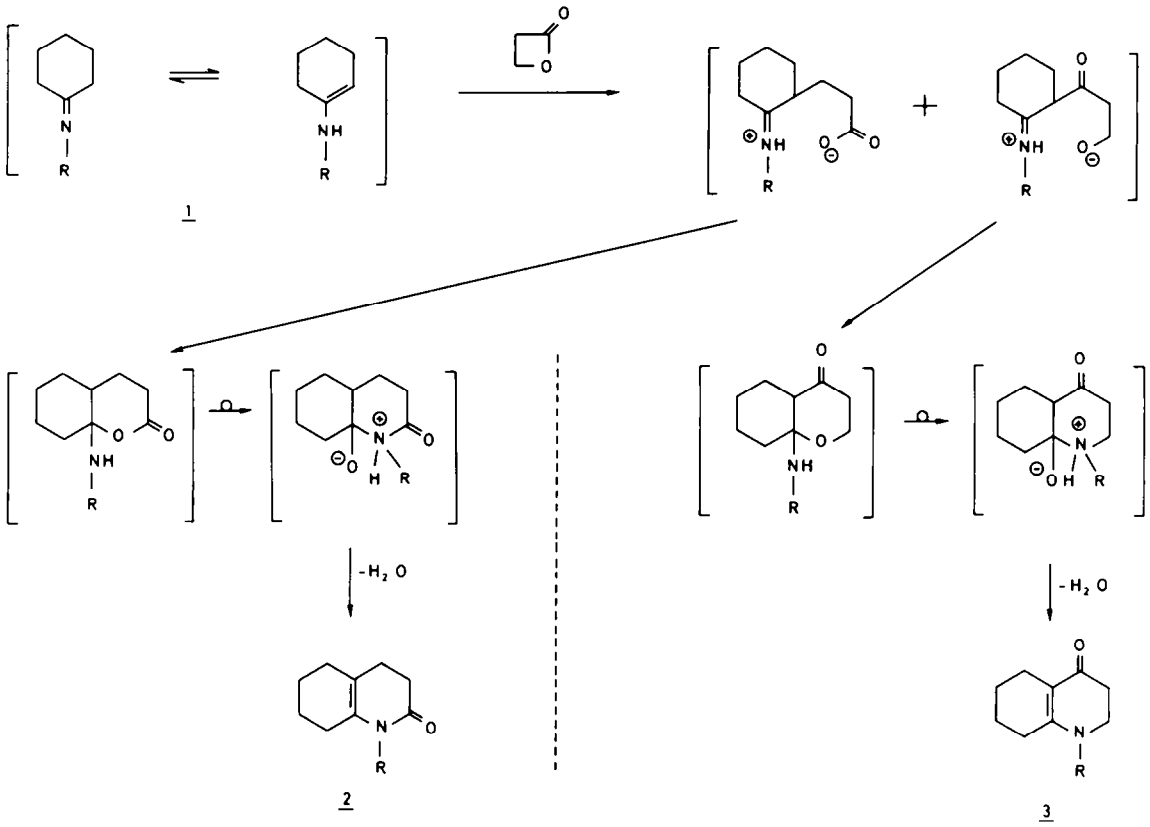
Compound **1a** was also reacted with crotonic acid, **6**, giving 4-methyl-N-phenyl-3,4,5,6,7,8-hexahydro-2-quinolinone, **2b**, and 2-methyl-N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinone, **3b**, and with 2-methacrylic acid, **7**, giving only 3-methyl-N-phenyl-3,4,5,6,7,8-hexahydro-2-quinolinone, **2c**. Due to steric hindrance **6** and **7** were expected to give lower yields of products. This was only observed with **7**. In the reaction between N-(cyclohexylidine)-4-chloro-aniline, **1d**, and β-propiolactone, **4**, or acrylic acid, **5**, the main products were N-(4-chlorophenyl)-2,3,5,6,7,8-hexahydro-4-quinolinone, **3d**, or N-(4-chlorophenyl)-3,4,5,6,7,8-hexahydro-2-quinolinone, **2d**, respectively, but in addition, 2-(4-chloroanilino)-propionic acid, **8**,[14] was isolated.

The formation of **8** is due to the reaction of **4** or **5** with 4-chloroaniline, a hydrolysis product from the imine, **1d**, which is more easily hydrolysed[15] than **1a**. Finally, N-(cyclohexylidine)-propylamine, **1e**, was reacted with both **4** and **5** giving only N-(propyl)-3,4,5,6,7,8-hexahydro-2-quinolinone.

†Part I see Ref. 12.

*On leave from The National Research Centre of Egypt, Dokki, Cairo.

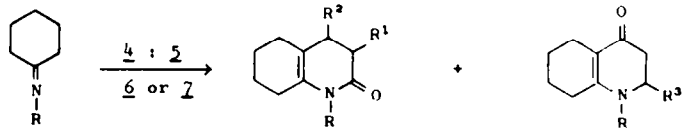
Scheme 2.



a: R=Ph d*: R=-⟨⟩-Cl e: R = n-propyl

*Besides 2d and 3d also 2-(4-chloroanilino)-propionic acid, 8, was isolated

Table 1. Results of the reaction between **1** and **4, 5, 6** or **7**



1 **2** **3**

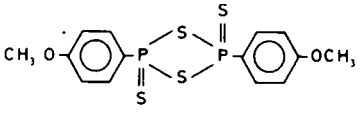
4: β-propiolactone, 5: acrylic acid, 6: crotonic acid, 7: 2-methacrylic acid

	R	R^1	R^2	R^3	Reaction compound	Reaction time/h	Yield of 2 (%)	Yield of 3 (%)
a	Ph	H	H	H	4	6	12	60
a	Ph	H	H	H	5	6	65	10
b	Ph	H	Me	Me	6	22	40	30
c	Ph	Me	H	Me	7	20	20	0
d*	p-Cl-Ph	H	H	H	4	3	0	50
d**	p-Cl-Ph	H	H	H	5	3	50	0
e	n-Pr	H	H	H	4	3	30	0
e	n-Pr	H	H	H	5	3	35	0

* 18% of 8 were isolated.

** 40% of 8 were isolated

Thiation of enaminones. It has been found that 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, **9**, is a most effective thiation reagent for ketones,[16] carboxamides,[17-21] esters,[22,23] S-substituted thionesters,[22] lactones,[24] lactams[25] and imides.[25]



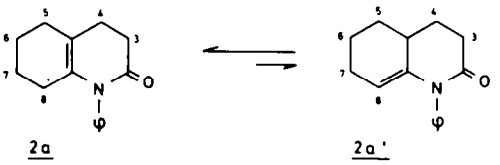
9

Because of the vinylogous effect enaminones show great similarities with carboxamides and lactams. The reaction of **9** with enaminones at room temperature was finished in less than 1 hr giving high yields of enaminothiones in most cases (Table 2 and 3). At elevated temperatures the yields are low probably due to polymerisation.[7]

Structure and spectroscopy. All compounds were characterized by the means of MS, IR, ^{1}H NMR, ^{13}C NMR and elementary analyses. Compound **2a** is known,[26] but no proof of structure has been given. The compounds **3a** and **10a** are unknown. As illustrative examples the ^{1}H NMR and ^{13}C NMR data of these three compounds are collected in the Tables 4 and 5. The assignments are made by selective decoupling technique.

It is surprising that only four allylic protons are observed. As seen from the ^{1}H NMR data the protons at C-8 are shifted up-field. This is due to the neighbouring phenyl group.

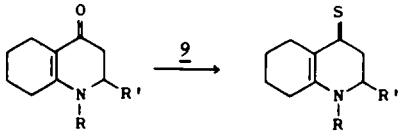
On prolonged standing in $CDCl_3$ solution a recorded 360 MHz ^{1}H NMR spectrum of **2a** also showed a resonance of the C-8 proton at 4.56 ppm demonstrating that the following equilibrium exists:



2a **2a'**

A similar equilibrium is not observed for **13a**.

Table 2. Thiation of cyclic enaminones



3 **10**

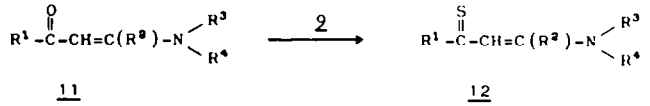
	R	R'	Yield (%)
a	Ph	H	95
b	Ph	Me	88
c	p-Cl-Ph	H	70

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer and the ^{13}C NMR spectra on a Varian CFT-20 spectrometer, except for **2a**, **3a**, **10a** and **13a** which were recorded at 360 MHz and 90.25 MHz, respectively, on a Bruker HX 360 spectrometer. TMS was used as internal reference and chemical shifts in δ-values. $CDCl_3$ was used as solvent. IR spectra were recorded on a Beckmann IR-18A spectrometer. Elementary analyses were carried out by NOVO-microanalytical Laboratory, NOVO Industry AS, NOVO Allé, DK-2880 Bagsværd, supervised by Dr. R. F. Amsler. Silicagel 60 (Merck) was used for column chromatography. M.ps are uncorrected.

Starting materials. The imines **1a** and **1b** were prepared by the condensation of the aromatic amine with cyclohexanone

Table 3. Thiation of non-cyclic enaminones



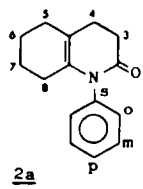
11 **12**

	R^1	R^2	R^3	R^4	Yield of 12 (%) lit.	M.p.	δ(C=S)/ppm
a	Me	Me	H	H	20**	oil**	209.3
b	Me	Me	Ph	H	63*	64	207.4
c	Ph	H	$-CH_2(CH_2)_3CH_2-$		58[5]	128	213.0
d	Ph	H	$-CH_2(CH_2)_2CH_2-$		92[5]	146	210.3

* Optimal separation procedure not yet found.

** B.p.$_{0.8}$ 120°C.

Table 4. ^{1}H NMR and ^{13}C NMR data of compound **2a**



2a

^{1}H NMR		^{13}C NMR	
H	ppm	C	ppm
		s	132.02
o	7.13	o	128.45
m	7.38	m	129.13
p	7.30	p	128.04
		8a	138.41
		2	170.22
3	2.64	3	32.11
4	2.26	4	25.61
		4a	114.65
5	2.12	5	28.98
6	1.56	6(7)	22.86
7	1.56	7(6)	22.27
8	1.65	8	26.98

and K_{10}† as catalyst (azeotropic removal of water with toluene).[27] **2e** was formed by condensation of n-propylamine with cyclohexanone at room temp, and removal of water with molecular sieves (Linde 5A).[28] Compounds **11a**,[29] **11b**,[29] **11c**,[30] and **11d**[30] were prepared according to known methods.

General procedure for the reaction of imines with α,β-unsaturated acids and β-propiolactone. The imine (0.02 mol) was dissolved in 10 ml dry chlorobenzene, and the α,β-unsaturated acid (or β-propiolactone) (0.02 mol) was dissolved in 5 ml dry chlorobenzene and added dropwise to the imine at room temp (½ hr) and then refluxed for different times (Table 1). After the reaction was complete (tlc), the solvent was evaporated under reduced pressure using rotatory-evaporator, and then the products were separated on silica-gel columns (ether/light petroleum).

General procedure for the preparation of enamino-thiones. The enaminone (0.01 mol) were reacted with the dimer **9** (0.005 mol) in dry benzene at room temp until no more of the enaminone was present (tlc). Reaction times ranged from 15–60 min. After filtration and evaporation of the solvent, the residue was placed on a silica-gel column and products eluted, first with a few ml benzene and then with ether/light petroleum (50/50).

Compound **13a**. N-phenyl-3,4,5,6,7,8-hexahydro-2-quinolin-thione. 0.01 mol **2a** was reacted with 0.005 mol **9** in toluene at 80°C for 1 hr. The solvent was evaporated and the residue was placed on a silica-gel column and eluted with ether/petroleum ether (light) 50/50, yield. 98%, m.p. 107–108°. **13a** was characterized by the means of MS, IR, ^{1}H NMR and ^{13}C NMR besides microanalyses. (Found: C, 73.20; H, 7.16; N, 5.68; S, 13.18%. Calc. for: C, 74.07; H, 7.00; N, 5.76; S, 13.17%). δ (C=S)/ppm 200.34.

Acknowledgements—Thanks are expressed to DANIDA for a fellowship to one of us (R.S.) and to Prof. H. Fritz, Ciba-Geigy, Basel, and Dr. S. Scheibye for the 360 MHz spectrum. After this investigation was finished we were informed by Prof. Walter, Hamburg, that his group had used **9** for the preparation of enamino-thiones.[31]

Table 5 ^{1}H NMR and ^{13}C NMR data of the compounds **3a** and **10a**

	^{1}H NMR (ppm)			^{13}C NMR (ppm)		
ASS.	3a	10a	Δ	3a	10a	Δ
o	7.15	7.20	0.05	126.90	126.41	-0.49
m	7.39	7.46	0.07	129.24	129.79	+0.55
p	7.28	7.38	0.10	126.90	128.07	1.17
s				145.20	144.04	-1.16
8a				159.16	157.22	-1.94
2	3.80	3.75	-0.05	52.03	51.82	-0.21
3	2.59	3.18	0.59	36.51	43.28	6.77
4				191.19	210.71	19.52
4a				109.06	122.79	13.73
5	2.37	2.72	0.35	21.89	27.98	6.09
6	1.56	1.65	0.09	22.52	22.67	0.15
7	1.56	1.59	0.03	22.17	22.26	0.09
8	2.02	2.09	0.07	29.30	30.15	0.85

Δ ppm = 10a (ppm) - 3a (ppm)

†K_{10} is an acidic catalyst of unknown composition kindly supplied by Sud-Chemie A. G München.

Table 6. Physical and analytical data of bicyclic lactams, **2**, enaminones, **3**, and the corresponding enaminothiones

Comp.	Mp/°C	δ/ppm $^{13}C(C=O)$	Analyses (%) Calc. (Found) C	H	N	Cl	S
2a	118	170.2	Known, lit.[32]				
3a	101	191.2	79.29 (79.12	7.49 7.50	6.17 6.13)		
2b	oil	179.9	79.67 (79.44	7.88 7.80	5.81 5.69)		
3b	135	191.1	79.67 (79.27	7.88 7.90	5.81 5.69)		
2c	oil	179.5	79.67 (78.45	7.88 7.88	5.81 5.58)		
2d	131	170.1	68.83 (68.48	6.12 6.16	5.35 5.60	13.58 13.58)	
3d	97	191.0	68.83 (68.87	6.12 6.11	5.35 5.39	13.58 13.48)	
2e	oil	170.0	74.57 (73.60	9.91 9.92	7.25 7.40)		
10a*	127	210.7	74.07 (73.26	7.00 6.99	5.76 5.67		13.1? 13.28)
10b*	146	208.8	74.66 (73.86	7.44 7.52	5.44 5.32		12.46 12.29)
10c*	157	211.8	64.85 (63.43	5.80 5.91		12.76 11.97	11.54 11.08)

* δ/ppm $^{13}C(C=S)$

REFERENCES

[1]G. Schroll, P. Klemmensen and S.-O. Lawesson, *Arkiv Kemi* **26**, 317 (1967).
[2]J. Bignebat, H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. Fr.* 1699 (1966).
[3]G. Duguay, H. Quiniou and N. Lozac'h, *Ibid.*, 4485 (1967).
[4]J. Bignebat, H. Quiniou and N. Lozac'h, *Ibid.* 127 (1969).
[5]F. Clesse and H. Quiniou, *Ibid.*, 1940 (1969).
[6]G. Duguay and H. Quiniou, *Ibid.*, 1918 (1970).
[7]K. Kamienska-Trela, U. Dabrowska and J. Dabrowski, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* 549 (1971).
[8]G. Duguay, C. Metayer and H. Quiniou, *Bull. Soc. Chim. Fr.*, 2507 (1974).
[9]J.-P. Pradere and H. Quiniou, *Ann. Chem. Ital* **63**, 563 (1973).
[10]J.-P. Pradere, Y. T. N'Guessan and H. Quiniou, *Tetrahedron* **31**, 3059 (1975).
[11]J. C. Meslin, Y. T. N'Guessan and H. Quiniou, *Ibid* **31**, 2679 (1975).
[12]S. O. Olesen, J. Ø. Madsen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 535 (1978).
[13]A. R. Olson and J. L. Hyde, *J. Am. Chem. Soc.* **63**, 2459 (1941).
[14]C. D. Hurd and S. Hayao, *Ibid.* **74**, 5889 (1952).
[15]R. L. Reeves, *Ibid.*, **84**, 3332 (1963).
[16]B. S. Pedersen, S. Scheibye, N. H. Nilsson and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 223 (1978).
[17]S. Scheibye, B. S. Pedersen and S.-O. Lawesson, *Ibid.* **87**, 229 (1978).
[18]S. Scheibye, B. S. Pedersen and S.-O. Lawesson, *Ibid.* **87**, 299 (1978).
[19]H. Fritz, P. Hug, S.-O. Lawesson, E. Logemann, B. S. Pedersen, H. Sauter, S. Scheibye and T. Winkler, *Ibid.* **87**, 525 (1978).
[20]K. Clausen, B. S. Pedersen, S. Scheibye, S.-O. Lawesson and J. H. Bowie, *Org. Mass Spectrometry* **14**, 101 (1979).
[21]K. Clausen, B. S. Pedersen, S. Scheibye, S.-O. Lawesson and J. H. Bowie, *Int. J. Mass Spectrom. Ion Phys.* **29**, 223 (1979).
[22]B. S. Pedersen, S. Scheibye, K. Clausen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 293 (1978).
[23]B. S. Pedersen and S.-O. Lawesson, *Tetrahedron* **35**, 2433 (1979).
[24]S. Scheibye, J. Kristensen and S.-O. Lawesson, *Ibid.* **35**, 1339 (1979).
[25]R. Shabana, S. Scheibye, K. Clausen, S. O. Olesen and S.-O. Lawesson, *Nouv. J. Chem.* **4**, 47 (1980).
[26]S. G. Agbalyan and A. O. Nshanyan, *Arm. Khim. Zh.* **22**, 425 (1969).
[27]C. Hansch, F. Gschwend and J. Bamberger, *J. Am. Chem. Soc.* **74**, 4554 (1952).
[28]K. Taguchi and F. H. Westheimer, *J. Org. Chem.* **36**, 1570 (1971).
[29]J. V. Greenhill, *J. Chem. Soc.* Perkin I, 2207 (1976).
[30]E. Benary, *Ber. Dtsch. Chem. Ges.* **63**, 1573 (1930).
[31]W. Walter and T. Proll, *Synthesis* 941 (1979).