signal des H aromatiques du produit de bromodésulfonation (tribromo-2,4,6-phénol): $\tau = 2{,}46$ ppm.

3. *Mise en évidence des intermédiaires B.* – a) *Par spectrophotométrie dans l'UV.* Conditions de mesure: [substrat introduit] = $1{,}30 \cdot 10^{-4}$ M; [Br_2 introduit] = $1{,}04 \cdot 10^{-4}$ M; [$HClO_4$] = $1{,}43 \times 10^{-2}$ M; solvant = H_2O.

Réaction de I (qui n'absorbe que faiblement au-dessus de 250 nm): pour l'intermédiaire B on a $\lambda_{max} = 261$ nm ($\varepsilon = 6000$).

Réaction de IV (qui n'absorbe que faiblement au-dessus de 250 nm): pour l'intermédiaire B on a $\lambda_{max} = 278{,}5$ nm ($\varepsilon = 11\,200$).

b) *Par spectrométrie de RMN.* Conditions de mesure: [substrat introduit] = 0,35 M; [Br_2 introduit] = 0,21 M; [NaBr] = 0,07 M; [HBr] = 0,05 M; solvant = D_2O; température $-1{,}5° \pm 0{,}1°$; référence interne = H_2O.

Réaction de I: intermédiaire B: $\delta = -130$ cps (H du cycle) et $\delta = +191$ cps (groupes CH_3); I: $\delta = -148$ cps (H aromat.) et $\delta = +173$ cps (groupes CH_3).

Réaction de IV: intermédiaire B: $\delta = -175$ cps (H du cycle); IV: $\delta = -178$ cps (H aromat.).

L'auteur exprime à M. le Professeur H. DAHN de l'Université de Lausanne, ainsi qu'à M. le Professeur H. ZOLLINGER de l'Ecole Polytechnique Fédérale de Zurich, sa sincère gratitude pour les précieux conseils qu'ils lui ont prodigués au cours de la réalisation de ce travail; il remercie vivement le FONDS NATIONAL SUISSE DE LA RECHERCHE SCIENTIFIQUE de l'appui financier qu'il lui a accordé.

BIBLIOGRAPHIE

[1] L. G. CANNELL, J. Amer. chem. Soc. *79*, 2927, 2932 (1957).
[2] H. DAHN & J.-D. AUBORT, Helv. *51*, 1537 (1968).
[3] LABORATORIES OM S.A., Ind. Pat. 70.219, Chem. Zbl. *33*, 1496 (1964).
[4] R. H. DEWOLFE & W. G. YOUNG, Chem. Rev. *56*, 786 (1956).
[5] A. STREITWIESER JR., Chem. Rev. *56*, 650 (1956).
[6] J. HINE, «Physical Organic Chemistry», 2e ed., p. 161, McGraw-Hill, New-York 1962.
[7] P. KARRER & P. LEISER, Helv. *27*, 680 (1944).
[8] E. CHAMBERS & G. W. WATT, J. org. Chemistry *6*, 379 (1941).
[9] M. J. ALLAIN-LE CANU, Bull. Soc. chim. France [2] *47*, 881 (1887).

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240. (4-Phenyl-2-thiazolyl)-acetone and its Enamines: Synthesis and NMR. Spectra[1][2]

by **T. R. Govindachari, S. Rajappa** and **K. Nagarajan**
CIBA RESEARCH CENTRE, Goregaon East, Bombay 63, India

(11. IX. 68)

Summary. The synthesis of (4-phenyl-2-thiazolyl)-acetone and its enamines is reported. Their NMR. spectra are discussed.

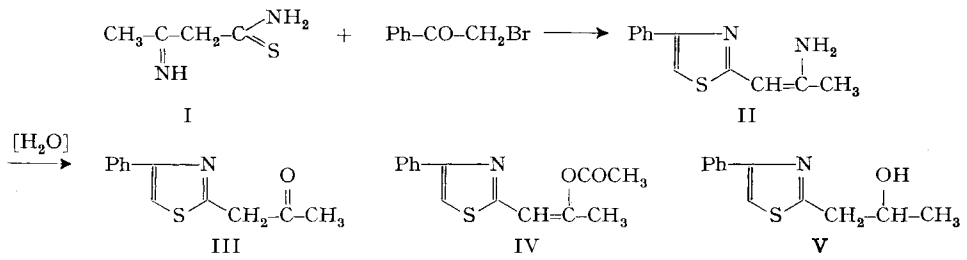
Synthesis. – The reaction of thioamides with α-bromoketones such as phenacyl bromide to form 2-substituted thiazoles is well-known [1]. It was of interest to find out how β-imino-thiobutyramide (I) would react under the same conditions. This compound has four nucleophilic centres, any two of which could react with the two

[1] Contribution No. 134 from CIBA RESEARCH CENTRE

[2] Vorgetragen am 28. Sept. 1968 an der Herbstversammlung der Schweiz. Chem. Gesellschaft und auf Englisch veröffentlicht laut besonderem Beschluss des Redaktionskomitees.

electrophilic sites of phenacyl bromide to form a cyclic product. In particular, we were interested in seeing whether a 7-membered ring could be obtained by this reaction.

In the event it turned out that the reaction occurred at the terminal thioamide group, leading to a disubstituted thiazole: When the reaction was carried out in boiling isopropanol, inorganic material (NH_4Br) crystallized out rapidly. The filtrate yielded well defined crystals of a low melting solid, $C_{12}H_{11}NOS$, IR. 1740, 1650 cm^{-1}, which was proved to be the ketone III arising from the enamine II by hydrolysis. –



Confirmation of this structure was achieved in two ways: acetylation of the base gave an enol-acetate IV, with IR. band at 1778 cm^{-1}. In the NMR. spectrum, the acetoxy methyl group appeared as a sharp singlet at 2.30 ppm, and the other methyl group as a doublet at 2.13 ppm (J = 1 cps); the olefinic proton with which this allylic coupling took place appeared as a quartet at 6.50 ppm (J = 1 cps). Sodium borohydride reduction of the ketone gave a non-crystalline alcohol V, whose NMR. spectrum revealed the methyl group as a doublet at 1.17 ppm (J = 6 cps), a methylene doublet at 2.97 ppm (J = 6 cps) and a methine multiplet at 4.17 ppm. A discussion of the NMR. spectrum of ketone III is deferred to a later section.

When the condensation of the thioamide I with phenacyl bromide was carried out in cold dry dioxan solution, the hydrobromide of the enamine II separated within a few minutes as a crystalline product. However, the solid rapidly decomposed in moist air, leaving within half an hour an oil. An IR. spectrum of the solid, taken within 5 minutes after filtration, showed a band at 1610 cm^{-1} and no carbonyl band at higher frequency. Treatment of the hydrobromide with triethylamine liberated the free base, $C_{12}H_{12}N_2S$. A detailed discussion of the NMR. spectrum of this base is given in a later section of this paper and shows that it has the enamine structure II rather than the tautomeric imino form.

Other enamines were prepared from ketone III by standard procedure.

Keto-enol tautomerism in thiazolyl-acetone III. – The NMR. spectrum of III in CCl_4, recorded in Fig. 1, showed two peaks of unequal intensity in the methyl region (2.00, 2.17 ppm) and two other bands at 4.00 and 5.48 ppm. Assuming that the aromatic region had 6 protons, the two methyl peaks *together* integrated for 3 H. The integrated intensities of the peaks at 4.00 and 2.17 ppm had approximately the ratio of 2:3, and those of the peaks at 5.48 and 2.00 ppm, the ratio 1:3. Further, the band at 2.00 ppm was actually a doublet ($J \sim 0.5$ cps) and the peak at 5.48 ppm a quartet with the same coupling constant. This is very similar to the allylic coupling in the enol-acetate IV. These data lead to the conclusion that in CCl_4, III exists as a mixture

of the keto (III a) and enol (III b) tautomers. Using the relative intensities of the methyl signals at 2.17 and 2.00 ppm, the keto-enol ratio can be calculated to be about 7:3. The presence of the olefinic signal in the CCl_4 spectrum could be accounted for by a third tautomeric structural possibility (III c); this is, however, ruled out, because this signal shows the proton to be allylically coupled to a methyl group. Long range coupling of this magnitude is not possible in systems of type III c [2].

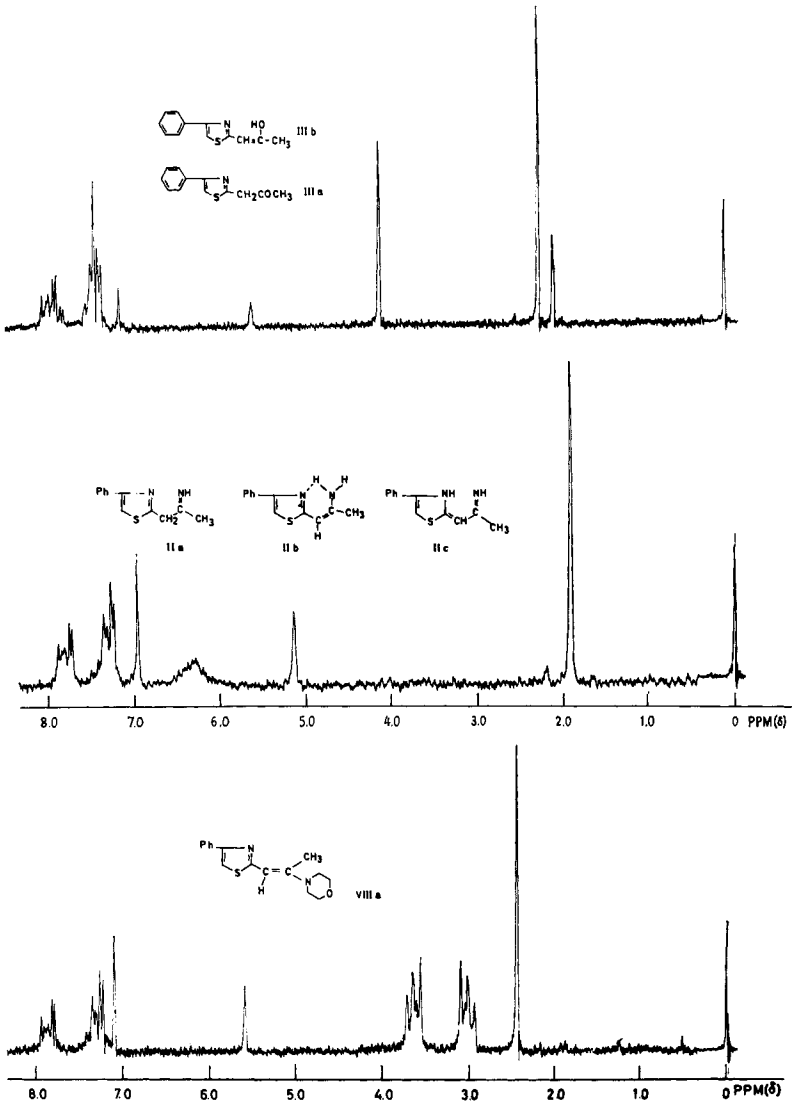
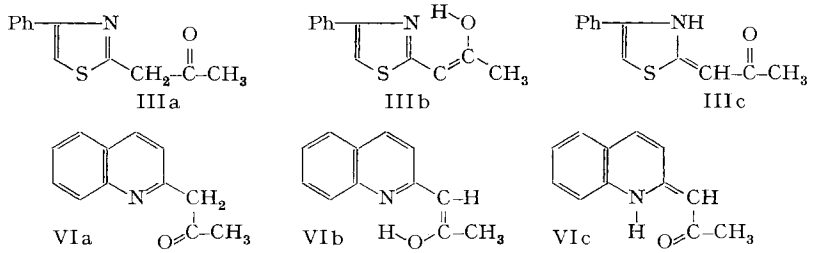


Fig. 1.
Top: *NMR. spectrum of (4-phenyl-2-thiazolyl) acetone (III)*
Middle: *NMR. spectrum of enamine IIb*
Bottom: *NMR. spectrum of enamine VIIIa*

Confirmation of the presence of the keto-enol equilibrium was provided on addition of D_2O to the CCl_4 solution. The two methyl signals remained essentially unchanged in intensity, whereas the methylene and methine protons disappeared, resulting from exchange with D.



In CCl_4 solution, benzyl methyl ketone was found to exist only in the ketonic form: methyl singlet (1.97 ppm), methylene singlet (3.55 ppm). The existence of about 30% enol form of III in CCl_4 solution can probably be attributed to increased stabilization of the enol by (i) intramolecular hydrogen bonding of –OH with the nitrogen or sulfur atom, and (ii) electron-withdrawal by the thiazole ring. No significant effect on the keto-enol ratio was observed in $CDCl_3$ over a concentration range of 5 to 10 mole percent.

As expected, increasing the dielectric constant of the solvent decreased the enol content as shown by data presented in Table I.

Table I. *Enol content of (4-phenyl-2-thiazolyl)-acetone (III) in various solvents*
(0.5 mmole in 5 mmole solvent)

Solvent	CCl_4	CS_2	$CDCl_3$	CH_2Cl_2	$(CD_3)_2SO$
Dielectric constant	2.24	2.64	4.81*)	9.08	47.0*)
% enol	29.3	32.5	14.2	13.6	11.6

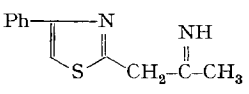
*) Values for undeuterated solvents

Keto-enol tautomerism in a few other heterocyclyl acetones has been studied recently [3]. Significantly, 2-quinolyl-acetone is shown to exist in CCl_4 predominantly as VIc (85%), the rest being accounted for by the keto form VIa; the enol form VIb was not detectable. In 2-pyridyl-acetone however, the presence of the enol could be demonstrated [3] [4].

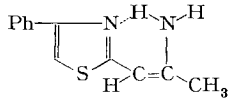
NMR. spectra of the enamines. – The NMR. spectrum of enamine II is reproduced in Fig. 1. There are three structural possibilities for this compound, IIa, IIb, and IIc. The absence of a methylene signal in the spectrum rules out IIa. Although allylic coupling of the methyl was not obvious as it was for the enol IIIb, it was noted that both the methyl and the olefinic signals had a greater line width than the tetramethylsilane and the thiazole proton signals. This would support structure IIb, rather than IIc. Further confirmation was obtained from the NMR. spectrum of the enamine VIIb of ketone III with benzylamine, wherein the benzylic methylene protons were seen as a doublet at 4.42 ppm (J = 6 cps). The coupling was with an NH proton[3]) as

[3]) Similar coupling in other enamines has been observed: see DUDEK & HOLM [5].

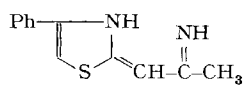
the doublet collapsed to a singlet when the enamine solution was treated with D_2O. Structures of type IIc, for these compounds are thus ruled out.



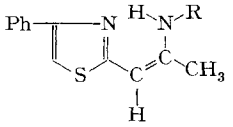
IIa

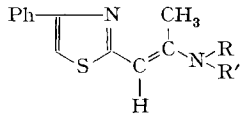


IIb

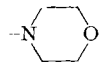


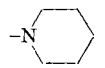
IIc

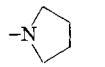


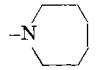


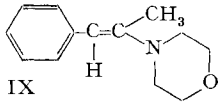
VIIa R = H (≡ IIb)
b R = CH_2Ph
c R = Ph

VIII  : a

 : b

 : c

 : d



IX

A few other interesting features which arose out of the NMR. studies of these and other enamines derived from III are discussed below.

Chemical shift of the methyl group: Early in our study, we noted that there was a marked downfield shift of the methyl signal in the NMR. spectrum (Fig. 1) of the morpholino-enamine VIIIa relative to its position in II. This prompted us to look at the spectra of a few different enamines of III. Table II summarises various chemical shift data gathered from these spectra.

Table II. *Chemical shifts in the NMR. spectra of the enamines VII and VIII*

Compound No.	Chemical Shift Data in ppm		
	Methyl group	Olefinic proton	Thiazole proton
VIIa	1.90	5.13	6.95
VIIb	1.95	5.17	6.87
VIIc	2.07	5.28	6.93
VIIIa	2.43	5.58	7.08
VIIIb	2.45	5.58	7.03
VIIIc	2.52	5.17	6.93
VIIId	2.55	5.37	6.95

As can be seen, the chemical shifts of the methyl groups allow the enamines to be classified into two groups: one with the methyl signal around 2.00 ppm (VIIa–c) and the second with the methyl signal around 2.5 ppm (VIIIa–d). We would suggest the following explanation: Under the conditions of preparation, the more stable geo-

metrical isomer of the enamine may be expected to be preferentially formed; in the case of the enamines derived from secondary amines, the more stable form would be VIII, having a *trans*-disposition of the amine and heterocyclic ring, allowing maximum conjugation. In the case of ammonia and primary amines, it is possible that the *cis*-isomer VII which permits hydrogen-bonding (either with the nitrogen atom as indicated, or with sulfur), is the more stable arrangement. The pronounced downfield shift of the methyl signal in VIII would then be ascribed to the hetero-aromatic ring current and/or the effect of the lone pair of electrons on the hetero-atom (nitrogen or sulfur).

In this connection, we would like to point out that the NMR. spectrum of the morpholino-enamine IX from benzyl methyl ketone [6], for which we would expect a *trans* arrangement, shows the methyl signal at 1.87 ppm. The methyl signals in *cis*- and *trans*-propenyl-benzenes also differ in their chemical shifts by only 0.05 ppm [7].

Chemical shift of the olefinic proton: Both electronic and steric factors associated with the amine component can be expected to influence the chemical shift of the vinyl proton in the enamines VII and VIII. Increased electron release into the olefinic system will result in an upfield shift of the olefinic proton [8]. Column 3 of Table II shows that the olefinic signal in the anilino-enamine VIIc is at 5.28 ppm, whereas the corresponding signals in VIIb and VIIIc are both at 5.17 ppm. This is in accordance with the order of basicity of the amine components (p*Ka* of aniline – 4.58; of benzylamine – 9.37; of pyrrolidine – 11.11), although the effect is not very pronounced. However, the olefinic signal in the piperidino-enamine VIIIb was at 5.58 ppm, 0.41 ppm lower field than it was in VIIIc. Since the p*Ka* of piperidine (11.21) signifies that it is as basic as pyrrolidine, an explanation has to be sought on steric grounds. It is known [9] that N-phenyl-piperidine is a stronger base than N-phenyl-pyrrolidine; this has been attributed to the inability of a 6-membered ring to support an exocyclic doube bond [8] [9] [10]. This results in decreased conjugation of the nitrogen atom with the aromatic ring in N-phenyl-piperidine, as compared to the conjugation existing in N-phenyl-pyrrolidine. The effect of a similar decreased electron-release from the piperidine nitrogen in VIIIb will then be displacement of the olefin signal to lower field as compared to VIIIc. In the case of the morpholino enamine VIIIa, again one would expect decreased conjugation, which accounts for the observed chemical shift of the olefinic proton (5.58 ppm). There is evidence in the literature [10] [11] that a seven-membered ring is intermediate between the five- and six-membered rings in its ability to support an exocyclic double bond. The chemical shift of the vinyl hydrogen in the hexamethylenimino-enamine VIIId is accordingly intermediate between those of VIIIb and VIIIc. It is interesting to note that no significant difference has been noted in the chemical shifst of the olefinic protons in 1-N-pyrrolidino- and 1-N-morpholino-cyclohexenes [8].

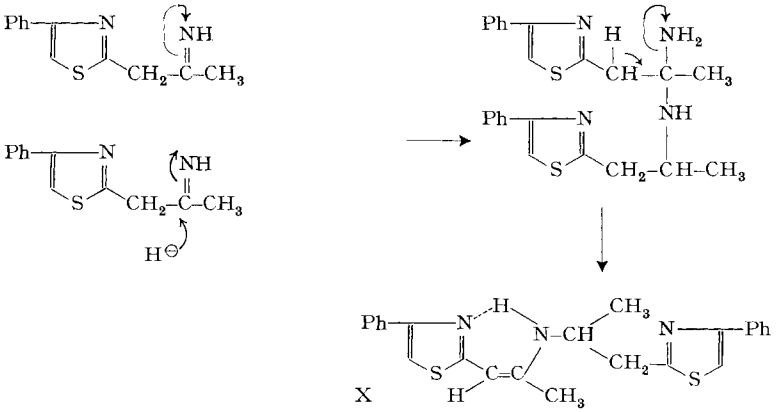
Similar effects on the chemical shifts of the thiazole proton, due to the basicity and ring size, may be expected. Inspection of column 4 of Table II shows that, with the apparent exception of VIIb, this expectation was realized, although the effects were smaller.

Structure of a dimeric reduction product. – The NMR. data which we had accumulated on the enamines proved to be valuable in elucidating the structure of a

novel compound that we obtained by sodium borohydride reduction of the hydrobromide of enamine II. The product, a beautifully crystalline compound, gave an analysis corresponding to $C_{24}H_{23}N_3S_2$. The NMR. spectrum (Fig. 2) showed the follow-

Fig. 2. *NMR. spectrum of dimeric reduction product X*

ing features: CH_3 doublet ($J = 6$ cps) at 1.42 ppm; CH_3 singlet at 1.98 ppm; CH_2 doublet ($J = 6$ cps) at 3.28 ppm; CH complex multiplet at about 4.13 ppm, losing part of its multiplicity on addition of D_2O; CH singlet at 5.20 ppm; one thiazole proton singlet at 7.00 ppm; one thiazole proton singlet at 7.33 ppm (?); 10 other aromatic protons at 7.20–8.00 ppm, and an NH doublet at 9.42 ppm, which was eliminated by D_2O. The only structure consistent with these data is X. Its formation can be envisaged as follows:



Experimental. – M.p.'s are uncorrected. NMR. spectra were taken in a VARIAN A-60 spectrometer with tetramethylsilane as internal standard. Chemical shifts are expressed as parts per million relative to tetramethylsilane.

4-Phenyl-2-thiazolyl-acetone (III): A mixture of phenacyl bromide (4.0 g) and β-imino-thiobutyramide [12] (2.3 g) in isopropanol (20 ml) was stirred and boiled under reflux for $^1/_2$ h. The solution was cooled, ammonium bromide filtered off, and the filtrate evaporated to dryness in vac. The residue was taken up in ether, washed with water, dried and evaporated. The product (2.4 g) was crystallised from ether/petrol, m.p. 50–52°.

$C_{12}H_{11}NOS$ Calc. C 66.35 H 5.10 S 14.74% Found C 65.93 H 5.23 S 14.61%

The enol-acetate IV: The ketone III (1.0 g) in dry pyridine (5 ml) was treated with acetic anhydride (15 ml) and left at room temperature overnight. The solution was then evaporated to

dryness in vac., the residue left standing with ice, and the solid filtered. Recrystallisation from aqueous alcohol gave the enol-acetate, m.p. 72–74°.

$C_{14}H_{13}NO_2S$ Calc. C 64.86 H 5.05 N 5.40% Found C 65.09 H 5.18 N 5.50%

The alcohol V: The ketone III (0.5 g) in isopropanol (15 ml) was treated with sodium borohydride (0.1 g). After $1^1/_2$ h at room temperature, the solvent was removed in vac., water was added, and the product extracted with ether. Evaporation of the ether left the alcohol V as an oil.

The enamine IIb: To a stirred, ice-cooled solution of β-imino-thiobutyramide (I) (2.3 g) in dry dioxan (30 ml) phenacyl bromide (4.0 g) was added in dioxan (15 ml). The ice-bath was then removed and after the solution attained room temperature, triethylamine (2.0 g) was added. The solution was filtered and the filtrate evaporated to dryness. The residue was taken up in ether and filtered to remove some insoluble material. Addition of hexane to the ether solution gave the enamine IIb, m.p. 96–98° after softening at 91°.

$C_{12}H_{12}N_2S$ Calc. C 66.65 H 5.59 N 12.96% Found C 66.86 H 5.78 N 12.89%

Other enamines (VII and VIII) were prepared from the ketone III by the standard procedure in boiling toluene with a trace of *p*-toluenesulfonic acid (see Table III).

Table III. *Some physical and analytical properties of the enamines VII and VIII*

Compound	Formula	m.p.	Analysis					
			Found			Calculated		
			C	H	N	C	H	N
VIIb	$C_{19}H_{18}N_2S$	116–120° softening at 110°	74.11	6.27	9.49	74.49	5.92	9.15
VIIc	$C_{18}H_{16}N_2S$	77–78°	73.97	5.64	9.84	73.95	5.52	9.58
VIIIa	$C_{16}H_{18}N_2OS$	100–104° softening at 95°	66.70	6.47	9.83	67.11	6.34	9.78
VIIIb	$C_{17}H_{20}N_2S$	75–82° *)	70.93	7.09	8.52	71.80	7.09	9.85
VIIIc	$C_{16}H_{18}N_2S$	83–84°	71.42	6.95	10.04	71.09	6.71	10.36
VIIId	$C_{18}H_{22}N_2S$	Oil						

*) NMR. spectrum indicated the presence of a small amount of ketone.

The dimeric reduction product X: The condensation of phenacyl bromide (4.0 g) and β-imino-thiobutyramide (2.3 g) was carried out in dry tetrahydrofuran. After 7 min, the enamine hydrobromide formed was quickly filtered and transferred to another flask containing anhydrous methanol. The solution was stirred and treated with sodium borohydride (0.8 g), followed by boiling under reflux for 3 h. The solution was then concentrated, cooled, and the solid filtered. Recrystallization from chloroform/petrol gave the dimer (1.9 g), m.p. 155–156°.

$C_{24}H_{23}N_3S_2$ Calc. C 69.05 H 5.55 N 10.07% Found C 68.88 H 5.74 N 10.21%

Acknowledgement. We are grateful to Dr. S. SELVAVINAYAKAM and his associates for analytical and spectral data, and to Messrs. V. S. IYER and S. R. MEHTA for technical assistance.

REFERENCES

[1] J. M. SPRAGUE & A. H. LAND, in «Heterocyclic Compounds» (R. C. ELDERFIELD, ed.), Vol. 5, p. 484, Wiley, New York 1957.
[2] K. TAKAHASHI, Bull. chem. Soc., Japan *37*, 963 (1964).
[3] R. MONDELLI & L. MERLINI, Tetrahedron *22*, 3253 (1966).
[4] G. KLOSE & E. UHLEMANN, in «Nuclear Magnetic Resonance in Chemistry», (B. PESCE, ed.), p. 237, Academic Press, London 1965.

[5] G.O.DUDEK & R.H.HOLM, J. Amer. chem. Soc. *83*, 2099 (1961), and subsequent papers.
[6] D.POCAR, G.BIANCHETTI & P.D.CROCE, Gazz. chim. ital. *95*, 1220 (1965).
[7] J.A.POPLE, W.G.SCHNEIDER & H.J.BERNSTEIN, «High Resolution Nuclear Magnetic Resonance», p.239, McGraw-Hill, New York 1959.
[8] G.STORK, A.BRIZZOLARA, H.LANDESMAN, J.SZMUSZKOVICZ & R.TERRELL, J. Amer. chem. Soc. *85*, 207 (1963).
[9] G.BADDELEY, J.CHADWICK & H.T.TAYLOR, J. chem. Soc. *1956*, 451.
[10] H.C.BROWN, J. chem. Soc. *1956*, 1248.
[11] E.L.ELIEL, «Stereochemistry of carbon compounds», p.267, McGraw-Hill, New York 1962.
[12] A.ADAMS & R.SLACK, J. chem. Soc. *1959*, 3061.

241. Essais de réactions dissymétriques sur quartz optiquement actif

par **Annie Amariglio, Henri Amariglio** et **Xavier Duval**

Laboratoire du Professeur X. DUVAL, Centre de 1er Cycle,
Boulevard des Aiguillettes, 54 Nancy

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Summary. – I. Three catalytical reactions are investigated (hydrogenation of methylethylketone, dehydrogenation and dehydration of 2-butanol) the catalyst being optically active quartz, either pure or metal covered. Emphasis is laid upon the most appropriate experimental conditions, generally neglected heretofore, when stereospecificity may be expected in a catalytic heterogeneous reaction. Numerous attempts under carefully controlled conditions have always led to negative results. Apparent optical rotations sometimes observed are shown to result from an extraneous effect due to minute quartz particles carried away with the reaction products.

II. Attempts to separate at room temperature various racemic modifications (2-butanol, cobalt or chromium complexes, ammonium tartrate) by liquid-solid chromatography on optically active quartz have always led to negative results. The resolution of (±)-2-butanol at dry ice temperature was also unsuccessful.

III. The failure to observe any asymmetric effect in catalysis as well as in adsorption on optically active quartz prompts to a critical analysis of previous work where small but positive effects have been claimed. It is shown that most of the small rotatory powers observed are within the limit of error of the measurements and that a number of results are inconsistent or unlike. These may have been vitiated by an extraneous effect which has been recognised and had been overlooked previously (dichroism or double refraction due to minute quartz particles suspended in the observed liquid).

I. RÉACTIONS CATALYSÉES

SCHWAB & RUDOLPH d'abord [1], TERENTJEW & KLABUNOWSKI plus tard [2 à 5] ont rapporté des résultats selon lesquels le quartz optiquement actif, utilisé comme catalyseur, seul ou recouvert de métal (catalyseur mixte), serait de nature à induire la dissymétrie dans une réaction chimique. Si la littérature [6 à 14] relate encore d'autres exemples illustrant le pouvoir stéréospécifique de ce catalyseur, elle mentionne également les échecs de plusieurs auteurs lors d'expériences nouvelles [9] [15] ou de tentatives en vue de reproduire certains des essais précédents [16].

Dans un article antérieur [17] nous avons analysé les travaux de synthèse asymétrique utilisant le quartz comme agent inducteur et avons constaté que l'action asymétrisante de ce minéral ne s'est jamais traduite que par une activité très faible du produit de la réaction.