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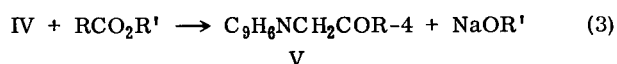
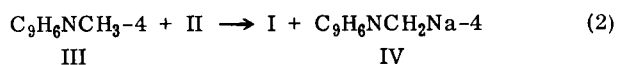
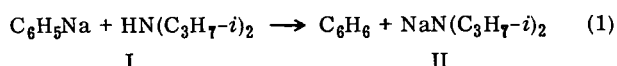
## The Acylation of Lepidine (I)

Burton M. Baum (2) and Robert Levine

A number of ketones have been prepared in good to high yields by acylating the methyl group of lepidine (III) with a variety of esters using sodium diisopropylamide (II) as the condensing agent. Two ketones, ethyl and isopropyl lepidyl ketone, have been shown to exist in two forms, the keto form and the intermolecular, hydrogen bonded, enolic form.

Recently it was demonstrated (3) that 3- and 4-picoline can be acylated in high yields using sodium diisopropylamide (SDIA) as the condensing agent. Since lepidine (III) has been condensed in only low to fair yields with ethyl benzoate (4) (44%), ethyl carbonate (4) (14%) and ethyl oxalate (4) (60%) and in unreported yield with ethyl acetate (5) using alkali amides as condensing agents, it appeared that SDIA (II) might be a better reagent than the alkali amides for effecting the acylation of III.

The reactions involved are summarized in the following equations where lepidine (III) is represented by  $C_9H_6NCH_3-4$ .

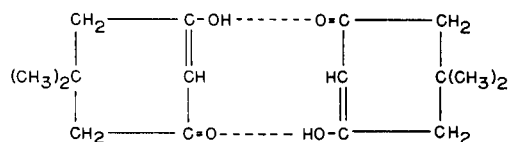


The yields of the acylation of III with a series of aliphatic, aromatic and heterocyclic esters appear in Table I. It can be seen that the yields are higher than those previously reported (4) with the alkali amides as condensing agents. In the acylations with the aliphatic esters, the highest yield (88%) was obtained with ethyl pivalate. The inability of this ester to self-condense (absence of  $\alpha$ -hydrogen atoms) may account for the higher yields than were obtained with esters which can self-condense. That a lower yield of ketone was obtained when methyl perfluoropropionate was used as the acylating ester than when ethyl pivalate was employed may be due to the possibility that the former ester, which has a very reactive carbonyl-carbon atom, was attacked to some extent at its carbonyl carbon atom by diisopropylamine and/or SDIA.

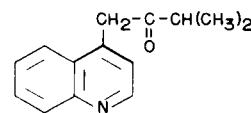
Two of these ketones, V ( $R = C_2H_5$  and  $i-C_3H_7$ ) have been shown to exist in two tautomeric forms (see experimental section).

Spectral data strengthen the hypothesis that the physical properties observed for isopropyl lepidyl ketone change when the ratio of keto to enol forms is altered. The infrared spectrum in chloroform

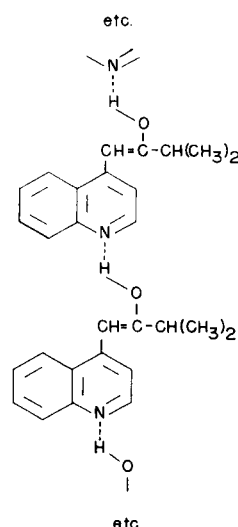
of the material melting at  $160-165^\circ$  exhibited absorption bands at  $2450-2300\text{ cm}^{-1}$  (broad),  $2050\text{ cm}^{-1}$ ,  $1950\text{ cm}^{-1}$ ,  $1625\text{ cm}^{-1}$ ,  $1540\text{ cm}^{-1}$  and  $1715\text{ cm}^{-1}$ , while the spectrum of the chloroform solution of the solid melting at  $45.5-46.6^\circ$  showed absorption at  $1700\text{ cm}^{-1}$  and had none of the bands described above. The spectra of the two solids



VI

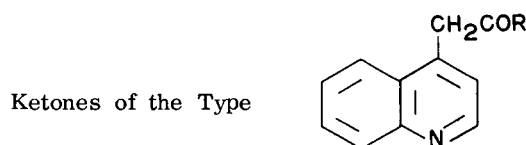


VII



VIII

TABLE I



Compound	R	Yield %	B. p. or M. p.		Formula	Carbon, %		Hydrogen, %		
			°C	mm.		Calcd.	Found	Calcd.	Found	
1	CH <sub>3</sub>	64.0	136-140 (a)	0.7-0.75	C <sub>12</sub> H <sub>11</sub> NO	77.81	77.61	5.99	6.24	
			71.8-72.6 (b)							
2	C <sub>2</sub> H <sub>5</sub>	68.0	134-135 (c)	0.55	C <sub>13</sub> H <sub>13</sub> NO	78.36	78.61	6.58	6.83	
3	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	65.9	133-135 (d)	0.50	C <sub>14</sub> H <sub>15</sub> NO	78.84	78.77	7.09	7.33	
4	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	58.0	140-143	0.75-0.80			78.97		7.17	
			45.4-46.6 (e)							
5	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	88.0	119-120 (f)		C <sub>15</sub> H <sub>17</sub> NO	79.26	79.00	7.54	7.60	
6	C <sub>2</sub> F <sub>5</sub>	65.0	255-256 (dec.) (g)		C <sub>13</sub> H <sub>8</sub> F <sub>5</sub> NO	53.99	54.25	2.79	2.70	
7	OC <sub>2</sub> H <sub>5</sub>	46.0	61.2-62.8 (b, h)							
8	C <sub>6</sub> H <sub>5</sub>	66.7	116.2-117.8 (i)							
9	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	83.1	127.4-129.0 (f)		C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub>	77.96	77.90	5.45	5.55	
10	2-C <sub>5</sub> H <sub>4</sub> N (j)	79.5	88.4-89.6 (f)		C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O	77.40	77.26	4.87	5.06	
11	2-C <sub>4</sub> H <sub>3</sub> O (k)	81.8	100.0-101.4		C <sub>15</sub> H <sub>11</sub> NO <sub>2</sub>	75.93	75.90	4.67	4.77	
12	2-C <sub>4</sub> H <sub>3</sub> S (l)	68.5	84.2-84.4 (a)		C <sub>15</sub> H <sub>11</sub> NOS	71.12	71.06	4.38	4.59	
Monopicrates										
1a			200.5-201.5 (m)		C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O <sub>8</sub>	52.18	52.41	3.41	3.60	
2a			199-200 (g)		C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O <sub>8</sub>	53.27	53.67	3.77	4.02	
3a			177-178 (g)		C <sub>20</sub> H <sub>18</sub> N <sub>4</sub> O <sub>8</sub>	54.30	54.43	4.10	4.54	
4a			191-192.5 (g)				54.33		4.04	
5a			206-207.5 (g)		C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O <sub>8</sub>	55.26	55.18	4.42	4.72	
6a			(n)							
7a			157 (g, o)							
8a			163.6-164.6 (g, p)							
9a			182.5-183.5 (g)		C <sub>24</sub> H <sub>18</sub> N <sub>4</sub> O <sub>9</sub>	56.92	57.06	3.58	3.88	
10a			204-205 (dec.) (g)		C <sub>22</sub> H <sub>15</sub> N <sub>5</sub> O <sub>8</sub>	55.35	55.71	3.17	3.43	
11a			194-195.5 (dec.) (g)		C <sub>21</sub> H <sub>14</sub> N <sub>4</sub> O <sub>9</sub>	54.08	54.21	3.03	3.34	
12a			190-191 (dec.) (g)		C <sub>21</sub> H <sub>14</sub> N <sub>4</sub> O <sub>8</sub> S	52.28	52.33	2.93	3.13	

(a) Literature value (see ref. 5), b.p. 117-119° at 0.02 mm. (b) Recrystallized from 30-60° petroleum ether. (c) The infrared spectrum indicates that this is a mixture of the keto form and the intermolecular, hydrogen bonded enolic form. (d) On exposure to air this ketone forms a monohydrate, m.p. 50° (from 30-60° petroleum ether); *Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>NO·H<sub>2</sub>O: C, 72.70; H, 7.41. Found: C, 72.43; H, 7.81. (e) See the experimental section about a discussion of the keto and enol forms of this compound. (f) Recrystallized from 60-70° petroleum ether. (g) Recrystallized from 95% ethanol. (h) W. Borsche and L. Büttschli, *Ann. Chem.*, 529, 266 (1937). (i) Recrystallized from a mixture of isopropyl ether and isopropyl alcohol; literature value (see ref. 4), m.p. 115.5-116°. (j) 2-C<sub>5</sub>H<sub>4</sub>N = 2-pyridyl radical. (k) 2-C<sub>4</sub>H<sub>3</sub>O = 2-furyl radical. (l) 2-C<sub>4</sub>H<sub>3</sub>S = 2-thienyl radical. (m) Literature value (see ref. 5), m.p. 202-203.5°. (n) Neither a carbonyl derivative nor a picrate could be formed. (o) Literature value (see ref. 4), m.p. 157°. (p) This is an oxime; literature value (see ref. 4), m.p. 165-166°.

are identical in the 1500-700  $\text{cm}^{-1}$  region. Based on somewhat comparable results which were obtained by Rasmussen *et al.*, (6) and Branch (7) with other ketonic and enolic systems, it appears that the higher melting solid has the characteristics of a conjugated enolic system, while the lower melting material has the characteristics of a ketonic structure.

It is of interest to note that Rasmussen and co-workers (6) found that the infrared spectrum of a chloroform solution of 5,5-dimethyl-1,3-cyclohexanedione exhibited absorption bands at 2632  $\text{cm}^{-1}$  and 1605  $\text{cm}^{-1}$  which they attributed to the intermolecular, hydrogen bonded structure (VI) since intramolecular hydrogen bonding is sterically inhibited.

It seems reasonable on the basis of spectral data to assign the ketonic structure (VII) to the lower melting form of isopropyl lepidyl ketone.

The higher melting solid probably consists of a mixture of VII and VIII, the conjugated, enolic, intermolecular hydrogen bonded structure. Its spectral band at 2450-2300  $\text{cm}^{-1}$  may be assigned to a hydrogen bonded hydroxyl group and the band at 1625  $\text{cm}^{-1}$  is probably due to carbonyl absorption. We are unable to assign the bands at 2050  $\text{cm}^{-1}$  and 1950  $\text{cm}^{-1}$  to any known group absorption. However, these bands may be characteristic of the intermolecular, enolic hydrogen bonded system in the lepidine series and appear in the spectrum which was taken of one other alkyl lepidyl ketone, *viz.*, ethyl lepidyl ketone.

It is also of interest to note that Amstutz and co-workers (8) have indicated that enolization occurs in certain quinoline derivatives which are quite similar to quinaldyl and lepidyl ketones. They (8) investigated the enolization of ethyl 2- and 4-quinolylpyruvate and concluded that the former compound contains enolic, chelate-like intramolecular hydrogen bonds and that the latter compound contains conjugated, enolic, intermolecular hydrogen bonds.

In view of the conjugated, enolic, intramolecular, chelate-like properties of 2-phenacylpyridine (6), it should be noted that the infrared spectrum of a chloroform solution of 4-phenylacetylquinoline (*i.e.*, phenyl lepidyl ketone) etc., exhibited only ketonic characteristics. However, a spectrum of 2-pyridyl lepidyl ketone in chloroform did exhibit the bands usually associated with enolic, hydrogen bond formation, but whether intramolecular or intermolecular hydrogen bonding is involved was not ascertained.

It has also been possible to carbethoxylate lepidine to give ethyl 4-quinolylacetate in 46% yield, which is considerably better than the 14% yield which was obtained using potassium amide as the condensing agent and a much longer reaction time (4).

## EXPERIMENTAL

### Preparation of Sodium Diisopropylamide.

This base was prepared by the addition of a solution of diisopropylamine in an equal volume of anhydrous benzene to phenylsodium (prepared from a sodium dispersion and bromobenzene) using the procedure described earlier (3).

### General Procedure for Acylating Lepidine (4-Methylquinoline).

Two equivalents of lepidine in an equal volume of anhydrous benzene were added to two equivalents of a suspension of sodium diisopropylamide keeping the temperature at 5°. An equivalent of the acylating ester in an equal volume of benzene was added and the mixture was treated as described earlier (3) for the acylation of 3-picoline and 4-picoline.

### Preparation of Isopropyl Lepidyl Ketone.

From the interaction of sodium diisopropylamide, (0.3 mole) of lepidine (0.3 mole, 43.0 g.) and ethyl isobutyrate (0.15 mole, 27.4 g.) there was obtained isopropyl lepidyl ketone (18.7 g., 58.0%, b.p. 140-143° at 0.75-0.80 mm.). Upon standing some of this oil solidified. When all of the material was redistilled and then cooled in a dry ice-acetone bath, an oily solid formed. Most of the solid dissolved in hot 30-60° petroleum ether. Upon cooling white cubic crystals precipitated, m.p. 45.4-46.6°; picrate, m.p. 191-192.5° (with decomposition) after recrystallization from 95% ethanol.

Some of the original oily solid could not be dissolved in hot 30-60° petroleum ether. This insoluble material was obtained as a white, powdery solid which melted initially at 160-165°. It was insoluble in ether and acetone and attempts to recrystallize it from ethanol-water mixtures failed. The melting point was increased greatly (up to 200°) when a portion of it was washed several times with acetone but it could not be obtained as a sharp melting solid. When a hot 30-60° petroleum ether solution of the material melting at 45.4-46.6° was seeded with this higher melting solid, only the lower melting solid crystallized. Upon standing the lower melting solid formed an oil. When the oil was dissolved in hot 30-60° petroleum ether, the lower melting form again crystallized. However, if the oil was washed with acetone or ether, then the higher melting solid precipitated.

The infrared spectrum of a chloroform solution of the solid melting at 160-165° showed the absorption characteristic of a conjugated, enolic, hydrogen bonded system (6) at 2450-2300  $\text{cm}^{-1}$  (broad), 1625  $\text{cm}^{-1}$  and 1540  $\text{cm}^{-1}$  and normal carbonyl absorption (9) at 1715  $\text{cm}^{-1}$ . In addition the spectrum exhibited absorption bands at 2050  $\text{cm}^{-1}$  and 1950  $\text{cm}^{-1}$  for which we have not been able to assign any known group absorption. The infrared spectrum of a chloroform solution of the solid melting at 45.4-46.6° indicated only the usual carbonyl absorption (9) at 1700  $\text{cm}^{-1}$  and none of the absorption bands described above. The spectra of the two solids are identical throughout the 1500-700  $\text{cm}^{-1}$  region. Apparently the lower melting solid is the keto form of the product while the higher melting material is a mixture of both the keto form and the intermolecular, enolic, hydrogen bonded form. Lepidine (23.0 g., 53.5%, b.p. 75-90° at 0.75 mm.) was recovered.

## REFERENCES

- (1) This work was performed under Contract AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.
- (2) This paper is based on part of a thesis presented by B. M. B. to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.
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