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SUBSTITUTED 3-PYRIDINECARBOXYLATES AND 3-ACYLPYRIDINES FROM 3-AMINOACROLEINS AND 1,3-DICARBONYL COMPOUNDS

E. BREITMAIER, S. GASSENMANN and E. BAYER
Chemisches Institut der Universität, D-7400 Tübingen

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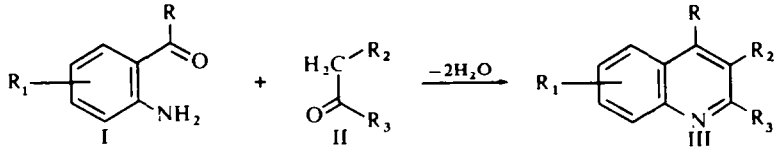
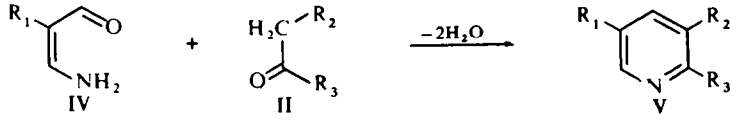
Abstract—A new general synthesis of 3-pyridinecarboxylates and 3-acylpyridines by cyclocondensation of 3-aminoacroleins with 1,3-dicarbonyl compounds is described.

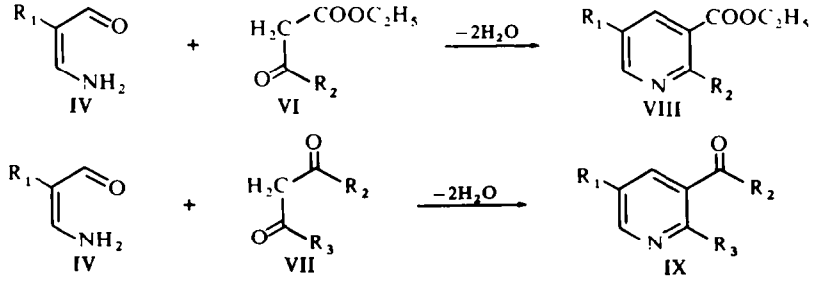
THE FRIEDLÄNDER synthesis of substituted quinolines (III) involves cyclocondensation of *o*-aminobenzaldehydes or *o*-aminophenones (I) with carbonyl compounds (II) containing methylene groups alpha to the carbonyl groups:[1-5]



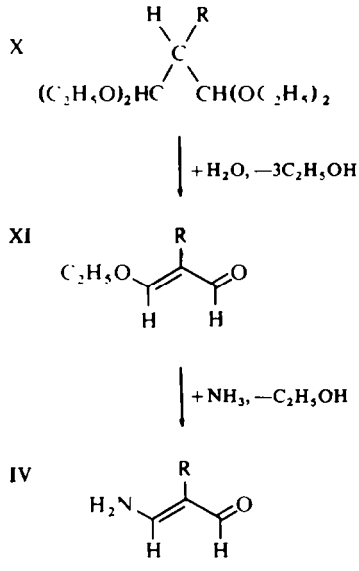
Our recently developed synthesis of substituted pyridines (V)[6] is based on a similar concept. Cyclocondensation of 3-amino-acroleins (IV) with α-CH_2-acidic carbonyl compounds (II) yields substituted pyridines (V):



Using this method, alkyl 3-pyridinecarboxylates (nicotinic acid esters) and 3-acylpyridines can be conveniently prepared. The cyclocondensation of 3-amino-acroleins (IV) with β-ketoesters (VI) yields substituted alkyl 3-pyridinecarboxylates (VIII) (Table 1). Similarly, substituted 3-acylpyridines (IX) are obtained by condensing 3-aminoacroleins (IV) with 1,3-diketones (VII) (Table 2):



A mixture of triethylamine and ammonium acetate is used as catalyst. The yields are between 50 and 80%. 3-Aminoacroleins (IV), required as starting materials, are prepared by hydrolysis of 1,1,3,3-tetraethoxypropanes (X) with aqueous *p*-toluenesulfonic acid[7] followed by ammonolysis of the resulting 3-ethoxyacroleins (XI):[8]



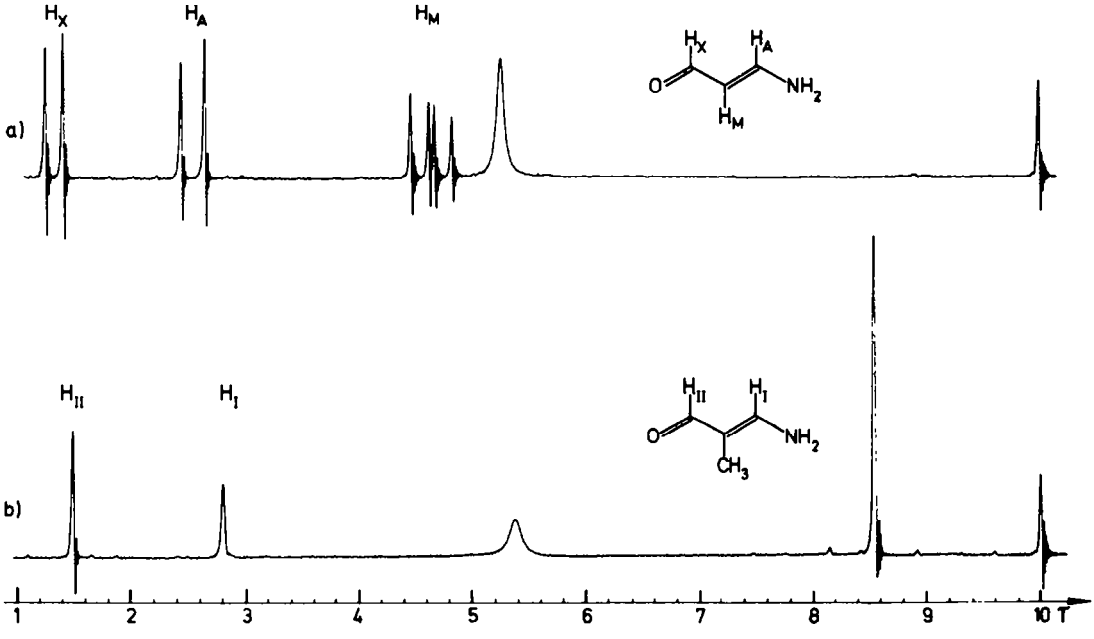


FIG 1. (a) 60 MHz ^{1}H-NMR spectrum of 3-aminoacrolein in D_2O relative to external TMS. (b) 60 MHz ^{1}H-NMR spectrum of 2-methyl-3-aminoacrolein in D_2O relative to external TMS.

The formation of the pyridine rings can be easily confirmed by means of the ^{1}H-NMR spectra of the reaction products. Fig 1a shows the AMX pattern of 3-aminoacrolein (IV, R...H) due to the group $—CH_A=CH_M—CH_X=0$. Fig 1b shows three singlets in the intensity ratio 1:3:1 due to the group $—CH=C(CH_3)—CH=0$ present in 2-methyl-3-aminoacrolein (IV, $R=CH_3$). In contrast, Figs 2a and b show the pyridine parts of the ^{1}H-NMR spectra of 2-ethyl-3-propionyl- and 2-ethyl-5-methyl-3-propionylpyridine (IXc and g) respectively. Fig 2a shows an ABX pattern arising from the pyridine protons in the 4-, 5- and 6-position. Fig 2b shows an AB pattern due to the pyridine protons in the 4- and 6-position.

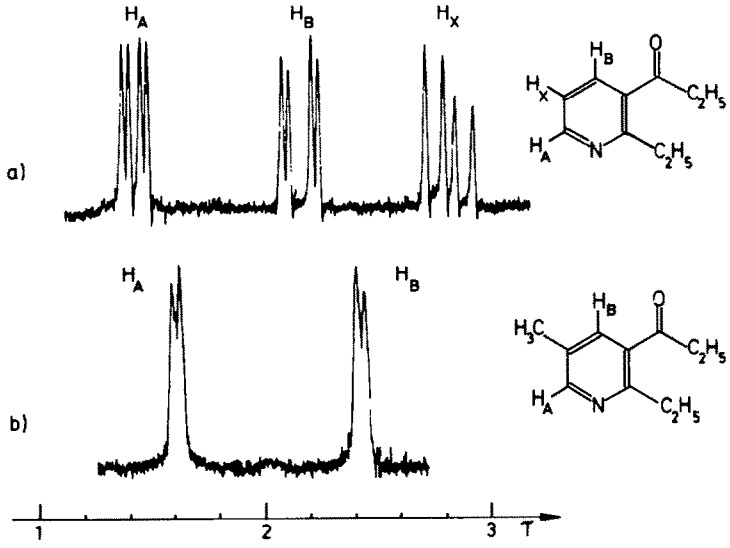


FIG 2. (a) 60 MHz ^{1}H-NMR spectrum of 2-ethyl-3-propionylpyridine in $CDCl_3$ relative to internal TMS. (b) 60 MHz ^{1}H-NMR spectrum of 2-ethyl-5-methyl-3-propionylpyridine in $CDCl_3$ relative to internal TMS.

EXPERIMENTAL

The β-ketoesters employed are obtained from EGA-Chemie, Steinheim/Albuch, Germany. Except for acetylacetone, which is as obtained from EGA-Chemie, Steinheim/Albuch, Germany, the 1,3-diketones employed are prepared according to Adams and Hauser.[9]

General preparation of 3-pyridinecarboxylates and 3-acylpyridines

0·15 moles of a β-ketoester (VI) (for preparation of 3-pyridinecarboxylates) or a 1,3-diketone (VII) (for preparation of 3-acylpyridines) is mixed with a 3-aminoacrolein (IV) (0·1 moles). After addition of powdered NH_4OAc (100 mg) and Et_3N (5 ml), the mixture is stirred and heated under reflux for 12 h in an oil bath kept at 110–120°. The brownish-red oily reaction mixture is poured into Et_2O (200 ml). The Et_2O soln is dried over $MgSO_4$ and filtered. The residue is washed with 3 × 50 ml portions of Et_2O. The Et_2O is evaporated from the combined filtrates on a rotatory evaporator. The oily product obtained is distilled under reduced pressure in a Zincke distillation apparatus. The fraction boiling 10° above and below the boiling point given in Table 1 or 2 is collected as the crude product and then fractionated on a 75 cm spinning band microcolumn (Normag, Hofheim/Main, Germany). The pyridines obtained are characterized by their m.ps and elemental analyses of their picrates as illustrated in Tables 1 and 2.

TABLE 1. 3-PYRIDINECARBOXYLATES FROM 3-AMINOACROLEINS AND β-KETOESTERS

Reactants	Product		Yield	B.P.	Picrate	
	VIII	Ethyl 3-pyridine-carboxylate	%	(mm Hg)	M.P.	Analysis % found (% calc)
3-Aminoacrolein, Ethyl 3-oxobutyrate	(a) $R_1 = H$ $R_2 = CH_3$	2-methyl-[10]	50	107–108° (12)	147 148°	C 46·43 (45·70) H 3·38 (3·55) N 14·48 (14·20) for $C_{15}H_{14}N_4O_9$
3-Aminoacrolein, Ethyl 3-oxovalerate	(b) $R_1 = H$ $R_2 = C_2H_5$	2-ethyl-	70	56–57° (0·05)	105- 106°	C 47·57 (47·00) H 4·08 (3·93) N 13·64 (13·73) for $C_{16}H_{16}N_4O_9$
3-Aminoacrolein, Ethyl 3-oxocaproate	(c) $R_1 = H$ $R_2 = nC_3H_7$	2-n-propyl-	60	55–56° (0·05)	100- 102°	C 48·53 (48·35) H 4·28 (4·26) N 13·38 (13·27) for $C_{17}H_{18}N_4O_9$
3-Aminoacrolein, Ethyl 4-methyl-3-oxovalerate	(d) $R_1 = H$ $R = CH(CH_3)_2$	2-iso-propyl-	60	50–51° (0·05)	143- 145°	C 48·11 (48·35) H 4·04 (4·26) N 13·48 (13·27) for $C_{17}H_{18}N_4O_9$
2-Methyl-3-aminoacrolein. Ethyl 3-oxobutyrate	(e) $R_1 = CH_3$ $R_2 = CH_3$	2,5-dimethyl-[11]	60	62–63° (0·05)	148–149°	C 47·29 (47·00) H 4·02 (3·93) N 13·89 (13·73) for $C_{16}H_{16}N_4O_9$
2-Methyl-3-aminoacrolein. Ethyl 3-oxovalerate	(f) $R_1 = CH_3$ $R_2 = C_2H_5$	2-ethyl-5-methyl-	65	63–64° (0·05)	124–125°	C 48·72 (48·35) H 4·41 (4·26) N 13·28 (13·27) for $C_{17}H_{18}N_4O_9$
2-Methyl-3-aminoacrolein. Ethyl 3-oxocaproate	(g) $R_1 = CH_3$ $R_2 = nC_3H_7$	2-n-propyl-5-methyl-	55	66–67° (0·05)	98–99°	C 50·26 (49·55) H 4·88 (4·59) N 13·01 (12·85) for $C_{18}H_{20}N_4O_9$
2-Methyl-3-aminoacrolein. Ethyl 4-methyl-3-oxovalerate	(h) $R_1 = CH_3$ $R_2 = CH(CH_3)_2$	2-iso-propyl-	50	54–55° (0·05)	147–148°	C 50·57 (49·55) H 4·02 (4·59) N 12·82 (12·85) for $C_{18}H_{20}N_4O_9$

TABLE 2. 3-ACYLPYRIDINES FROM 3-AMINOACROLEINS AND 1,3-DIKETONES

Reactants	Product		Yield	B.P.		Picrate
	IX	Pyridine	%	(mm Hg)	M.P.	% found (% calcd.)
3-Aminoacrolein, 2,4-Pentanedione	(a) $R_1 = H$ $R_2 = R_3 = CH_3$	2-Methyl-3-acetyl-[12]	55	104–105° (12)	176–177°	C 46·21 (46·18) H 2·95 (3·30) N 15·30 (15·36) for $C_{14}H_{12}N_4O_8$
3-Aminoacrolein, 2,4-Hexanedione	(b) $R_1 = H$ $R_2 = CH_3(C_2H_5)$ $R_3 = C_2H_5(CH_3)$	2-Methyl-3-propionyl- or 2-ethyl-3-acetyl-	75	47–48° (0·1)	127–128°	C 48·14 (47·63) H 3·53 (3·70) N 14·44 (14·80) for $C_{15}H_{14}N_4O_8$
3-Aminoacrolein, 3,5-Heptanedione	(c) $R_1 = H$ $R_2 = R_3 = C_2H_5$	2-Ethyl-3-propionyl-	75	56–57° (0·1)	126–127°	C 48·85 (48·98) H 4·18 (4·08) N 14·12 (14·27) for $C_{16}H_{16}N_4O_8$
3-Aminoacrolein, 4,6-Nonanedione	(d) $R_1 = H$ $R_2 = R_3 = nC_3H_7$	2-n-Propyl-3- n-butyryl-	70	73–74° (0·1)	100–102°	C 50·92 (51·47) H 4·66 (4·76) N 13·42 (13·33) for $C_{18}H_{20}N_4O_8$
2-Methyl-3-aminoacrolein, 2,4-Pentanedione	(e) $R_1 = CH_3$ $R_2 = R_3 = CH_3$	2,5-Dimethyl-3-acetyl-	80	71–73° (0·1)	174–176°	C 47·71 (47·63) H 3·81 (3·70) N 14·82 (14·80) for $C_{15}H_{14}N_4O_8$
2-Methyl-3-aminoacrolein, 2,4-Hexanedione	(f) $R_1 = CH_3$ $R_2 = CH_3(C_2H_5)$ $R_3 = C_2H_5(CH_3)$	2,5-Dimethyl-3-propionyl- or 2-ethyl-5-methyl- 3-propionyl-	70	62–63° (0·1)	126–127°	C 48·98 (48·98) H 4·01 (4·08) N 14·16 (14·27) for $C_{16}H_{16}N_4O_8$
2-Methyl-3-aminoacrolein, 3,5-Heptanedione	(g) $R_1 = CH_3$ $R_2 = R_3 = C_2H_5$	2-Ethyl-5-methyl- 3-propionyl-	80	72–73° (0·1)	119–121°	C 49·65 (50·25) H 3·81 (4·44) N 13·69 (13·80) for $C_{17}H_{18}N_4O_8$
2-Methyl-3-aminoacrolein, 4,6-Nonanedione	(h) $R_1 = CH_3$ $R_2 = R_3 = nC_3H_7$	2-n-Propyl-5-methyl- 3-n-butyryl-	60	75–76° (0·1)	88–89°	C 52·64 (52·50) H 4·83 (5·07) N 13·14 (12·90) for $C_{19}H_{22}N_4O_8$

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