[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

CLAISEN CONDENSATIONS OF ESTERS OF N-HETEROCYCLIC ACIDS. CONDENSATIONS OF ETHYL ISOQUINOLINE-4-CARBOXYLATE

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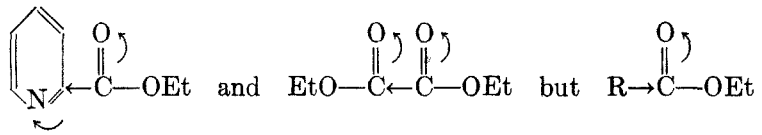
Condensations of esters of N-heterocyclic acids with compounds containing active methylene groups have been of importance in syntheses of several alkaloids. The condensations have frequently proceeded unexpectedly well (14), and a survey of the field now indicates that in general such condensations (Table I) have given yields somewhat better than those obtainable using esters of aromatic acids under comparable conditions.

Whatever superiority as acceptors the heterocyclic esters show is doubtless to be referred to the electronegativity of the heterocyclic nucleus.[1] The following symbols indicate an analogy in this respect between an ester of the type under discussion and ethyl oxalate, an ester known to be exceptionally active as an acceptor.



It appeared of some interest to study the behavior of ethyl isoquinoline-4-carboxylate in the Claisen reaction. In this molecule, the carbethoxyl group occupies a position of high electron density, as indicated by the preferential bromination of isoquinoline in the 4-position. Such a carbethoxyl group would be expected to be relatively inactive as an acceptor.[2] The present study has borne out this expectation. With ethyl acetate, ethylisoquinoline-4-carboxylate gave only 49% of crude I. With ethyl 1-benzoylpiperidine-4,β-propionate, there was obtained 68% of II, but this product was very impure, since on partial

[1] Craig and Hixon [*J. Am. Chem. Soc.*, **53**, 4371 (1931)] have stated that, "The dissociation constants of the picolylamines" (α- and β-) "indicate the pyridyl radical to be almost as much more negative than the phenyl as the phenyl is more negative than the saturated aliphatic radicals."

It is also noteworthy in this connection that C-alkylation of ethyl α-pyridylacetate in the presence of alcoholic potassium ethoxide has been carried out (30).

[2] This effect, although probably less noticeable in the pyridine series, accounts for the early observation by Ferenczy (3) that the condensation of ethyl picolinate with acetone took place easily and gave a good yield of pyridoylacetone, whereas it required a careful attention to detail to obtain a satisfactory yield in the condensation of ethyl nicotinate with acetone.

TABLE I

CONDENSATIONS OF N-HETEROCYCLIC ESTERS

METHYLENE COMPOUND	BASE AND CONDITIONS[a]	PRODUCT	YIELD,[b] %	REF.
Condensations with Ethyl Picolinate				
Acetone	NaOEt, benzene, 50° 1 hr.	diketone	75	2
Ethyl acetate	NaOEt, dry, 25° 24 hr.	keto ester	?	4
Ethyl acetate	NaOEt[c], dry, 25° 24 hr.	keto ester	44	15
Ethyl acetate	Na, benzene, hydrol.	ketone	50	26
Ethyl acetate	NaOEt, dry, hydrol.	ketone	50	26
Ethyl acetate	KOEt, benzene, 80° 6 hr.	keto ester	55	33
Ethyl acetate	NaOEt, EtOAc, b. 10 hr., hydrol	ketone	50	41
Ethyl propionate	NaOEt, dry, 25° 24 hr.	keto ester	?	4
Ethyl butyrate	NaOEt, dry, 25° several days	?	trace	4
Ethyl succinate	NaOEt, benzene, b. 1 hr. hydrol.[d]	γ-keto ester	35	20
Ethyl ethoxyacetate	?	?	trace	30
Butyrolactone	Na, benzene, b. 2 hr.	keto lactone	79x	25
Butyrolactone	NaOEt, benzene, b. 2 hr.	keto lactone	90x	25
γ-Ethoxymethyl-γ-butyrolactone	Na, benzene, b. 2 hr.	keto lactone	80x	35
Pyrrolidone	NaOEt, benzene	keto lactam	68x	25
N-Methylpyrrolidone	NaOEt, benzene, b. 8 hr.	keto lactam	93x	19
Succinimide	?	?	?	25
N-Methylsuccinimide	Na, benzene, b. 15 hr.	keto imide	91	25
Condensation with Ethyl 6-Methylpicolinate				
Ethyl acetate	NaOEt, dry, 25° 24 hr.	keto ester	?	4
Condensations with Ethyl 3,5-Dimethylpicolinate				
Ethyl propionate	NaOEt, benzene, b. 1 hr., hydrol.	ketone	52	31
Ethyl succinate	NaOEt, benzene, b. 1 hr., hydrol.[d]	γ-keto ester	50	31
Condensations with Ethyl Nicotinate				
Acetone	NaOEt, ether, 25° 12 hr.	diketone	55	3
Acetone	NaOEt, ether, 25° 1 hr.	diketone	45	22
Acetone	NaOEt, acetone, 56° 3 hr.	diketone	82	24
Acetone	NaOEt, xylene, 100° 4 hr.	diketone	63	27
Hexanone-2	NaOEt, xylene, 100° 4 hr.	diketone	46	27
4-Methylpentanone-2	NaOEt, xylene, 100° 4 hr.	diketone	70	27
Pinacolone	NaOEt, xylene, 100° 4 hr.	diketone	42	27
Heptanone-2	NaOEt, xylene, 100° 4 hr.	diketone	47	27
Pentadecanone-2	NaOEt, xylene, 100° 4 hr.	?	0	27
Acetophenone	NaOEt, xylene, 100° 4 hr.	diketone	70	27
Acetomesitylene	NaOEt, xylene, 100° 4 hr.	diketone	60	27
4-Acetobiphenyl	NaOEt, xylene, 100° 4 hr.	?	0	27

TABLE I—*Continued*

METHYLENE COMPOUND	BASE AND CONDITIONS[a]	PRODUCT	YIELD,[b] %	REF.
Condensations with Ethyl Nicotinate—*Continued*				
Ethyl acetate	NaOEt, dry, 25° 24 hr.	keto ester	?	4
Ethyl acetate	NaOEt, dry, 100° 1.5 hr., hydrol.	ketone	70	16
Ethyl acetate	NaOEt, EtOAc, b. 6 hr.	keto ester	70	21
Ethyl acetate	NaOEt, dry, 77° 2.5 hr.	keto ester	49	24
Ethyl acetate	NaOEt, xylene, 100° 4 hr., hydrol.	ketone	87	27
Ethyl acetate	NaOEt, EtOAc, b. 10 hr., hydrol.	ketone	81	41
N-Methylpyrrolidone	NaOEt, benzene, b. 8 hr.	keto lactam	70	17
N-Benzoylpyrrolidone	NaOEt, benzene, b. 24 hr., hydrol.	myosmine	13	28
N-Methylpiperidone	NaOEt, ligroin, b. 24 hr.	keto lactam	31	14
N-Benzoylpiperidone	NaOEt, benzene, b. 24 hr., hydrol.	anabaseine	52x	29
3-Acetopyridine	NaOEt, xylene, 100° 4 hr.	diketone	51	27
Condensation with Ethyl 4-Methylnicotinate				
Ethyl acetate	NaOEt, benzene, b. 5 hr., hydrol.	ketone	36	12
Condensation with Ethyl 2,6-Dimethylnicotinate				
Ethyl acetate	NaOEt, dry, 100° 6 hr., hydrol.	ketone	27	39
Condensation with Ethyl 6-Methoxynicotinate				
N-Methylpiperidone	?	?	0	11
Condensations with Ethyl Isonicotinate				
Acetone	NaOEt, ether, 25° 48 hr.	diketone	55	5
Acetophenone	NaOEt, ether, 25° 48 hr.	diketone	?	5
Ethyl acetate	NaOEt, dry, 25° 24 hr.	keto ester	?	4
Ethyl acetate	NaOEt, EtOAc, b. 10 hr., hydrol.	ketone	80	41
Ethyl acetate	NaOEt, ether, b. 4 hr.	keto ester	54	45
Condensations with Ethyl Quinaldinate				
Benzyl cyanide	$NaNH_2$, ether, b. 30 min.	keto nitrile	79	6
N-Methylpyrrolidone	Na, benzene, b. 7 hr.	keto lactam	?	25
N-Methylsuccinimide	?	?	0	25
Condensations with Ethyl Quinoline-3-carboxylate				
Ethyl acetate	NaOEt, benzene, b. 12 hr.	keto ester	80	40
N-Methylpyrrolidone	NaOEt, benzene, b. 9 hr.	keto lactam	47	38
Ethyl N-benzoylhomocincholoiponate	NaOEt, benzene, hydrol.	ketone	70	40

TABLE I—*Continued*

METHYLENE COMPOUND	BASE AND CONDITIONS[a]	PRODUCT	YIELD,[b] %	REF.
Condensations with Ethyl 2-Methoxyquinoline-3-carboxylate				
Ethyl acetate	NaOEt, benzene, b. 10 hr., hydrol.	ketone	32	40
Ethyl N-benzoylhomocincholoiponate	NaOEt, benzene, hydrol.	ketone	?	40
Condensation with Ethyl Cinchoninate				
Acetone	NaOEt, benzene, 60° 3 hr.	diketone	?	1
Ethyl acetate	NaOEt, benzene, b. 10 hr.	keto ester	?	7
Ethyl acetate	NaOEt, ether, b. 20 hr.	keto ester	85	45
Ethyl δ-(N-benzoyl-N-ethylamino)valerate	NaOEt, benzene, 65° 24 hr.	keto ester	58	14
Ethyl ε-aminocaproate	NaOEt, benzene, b. 48 hr.	keto ester	17x	14
Ethyl ε-benzoylaminocaproate	NaOEt, benzene, b. 48 hr.	keto ester	17	14, 32
Ethyl ε-benzoylaminocaproate	Na, benzene	keto ester	34[e]	32
Ethyl ε-benzoylaminocaproate	$NaNH_2$,[f] benzene, b. 7 hr.	keto ester	64	32
Ethyl ε-(N-benzoyl-N-methylamino)caproate	NaOEt, benzene, b. 48 hr.	keto ester	45	14
Ethyl tetrahydropyran 4,β-propionate	NaOEt, benzene, b. 16 hr., hydrol.	ketone	60	34
N-Methylpiperidone-2	NaOEt, ligroin, b. 12 hr.	keto lactam	60	11
N-Ethylpiperidone-2	NaOEt, ligroin, b. 12 hr.	keto lactam	63	11
Azepinone-2	NaOEt, benzene,[g] b. 48 hr.	? (mixture)	20	11
N-Methylazepinone-2	NaOEt, ligroin, b. 24 hr.	keto lactam	17	11
N-Benzoylazepinone-2	NaOEt, benzene, b. 24 hr.	keto lactam	30x	11
Ethyl 1-benzoylpiperidine-4,β-propionate	NaOEt, benzene, b. 3.5 hr.	keto ester	66	13
Ethyl N-benzoylhomocincholoiponate	NaOEt, benzene, b. 15 hr.	keto ester	40	9
Condensations with Ethyl 2-Methylcinchoninate				
Ethyl acetate	NaOEt, benzene, 80° 18 hr.	keto ester	53	36
Ethyl *cis*-4-acetylaminocyclohexylacetate	?	none	—	36
Condensation with Ethyl 2-Phenylquinoline-4-carboxylate				
N-Methylpiperidone-2	NaOEt, benzene	keto lactam	23	14
Condensation with Ethyl 2-Ethoxyquinoline-4-carboxylate				
Ethyl tetrahydropyran-4,β-propionate	NaOEt, benzene, b. 15 hr., hydrol.	ketone	48	34

TABLE I—*Continued*

METHYLENE COMPOUND	BASE AND CONDITIONS[a]	PRODUCT	YIELD[b],%	REF.
Condensations with Ethyl Quininate				
Acetone	NaOEt, benzene, 80° 1.5 hr.	diketone	?	47
Ethyl acetate	NaOEt, benzene, b. 20 hr.	keto ester	56	8
Ethyl propionate	NaOEt, benzene, b. 20 hr.	keto ester	30	7
Ethyl ϵ-benzoylamino-caproate	$NaNH_2$, benzene, b. 7 hr.	keto ester	36	32
Ethyl ϵ-benzoylamino-caproate	$NaNH_2$, toluene, b. 7 hr.	?	55	32
Ethyl ϵ-(N-benzoyl-N-methylamino)caproate	NaOEt, benzene, b. 48 hr.	keto ester	35	14
Ethyl *cis*-4-acetylamino-cyclohexylacetate	NaOEt, benzene, 80° 20 hr.	keto ester	30	36
Ethyl tetrahydropyran-4,β-propionate	NaOEt, benzene, b. 16 hr., hydrol.	ketone	40	34
N-Methylpiperidone-2	NaOEt, ligroin, b. 24 hr.	keto lactam	50	11
Azepinone-2	NaOEt, benzene, b. 48 hr.	keto lactam	3	14
Ethyl 1-benzoylpiperidine-4,β-propionate	NaOEt, benzene, b. 4 hr.	keto ester	50	13
Ethyl 1-benzoylpiperidine-4,β-propionate	NaOEt, dry, then hydrol.	ketone	90	42
Ethyl 1-benzoylpiperidine-4,β-propionate	Na, benzene, b. 4 hr.	keto ester	75x	43
Ethyl N-benzoylhomo-cincholoiponate	NaOEt, benzene, b. ? hr.	keto ester	55	10
Ethyl N-benzoylhomo-cincholoiponate	NaOEt, dry, then hydrol.	ketone	63	18
Ethyl N-benzoylhomo-cincholoiponate	? then hydrol.	ketone	?	23
Ethyl N-benzoylhomo-meroquinenate	NaOEt, dry, 90° 15 hr.	keto ester	59	44
Condensation with Ethyl 6-Methoxyquinoline-8-carboxylate				
Ethyl N-benzoylhomo-cincholoiponate	NaOEt, dry, 80° 4 hr.	keto ester	64	37

[a] In several instances the reagents were allowed to stand at room temperature for some time and then heated; only the latter process has been recorded in the table. The letter "b." means boiled. Often a crude condensation product was not isolated, but simply hydrolyzed and decarboxylated by boiling it with hydrochloric or hydrobromic acid; this is indicated in the table by "hydrol."

[b] The letter "x" refers to a crude product. Where yields in several similar experiments have been published in one place, only the highest has been recorded in the table.

[c] A poorer yield was obtained using metallic sodium.

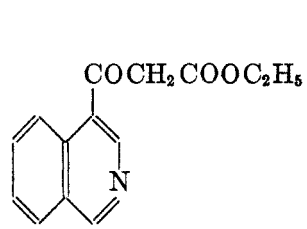
[d] The hydrolysis product was then re-esterified.

[e] When methyl esters were used under the same conditions, a yield of 25% was obtained.

[f] Yields are greatly reduced by traces of nitrite in the sodamide.

[g] Similar results were obtained using toluene or ligroin.

hydrolysis the keto ester gave only 26% of crude non-acidic decarbethoxylation product.



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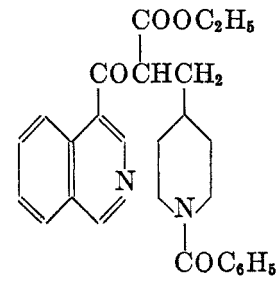

II

EXPERIMENTAL

4-Cyanoisoquinoline was obtained in a yield of 94% by the method of Tyson (46); it was found advantageous to hydrolyze this nitrile to the acid (yield 90%) by boiling it for thirty minutes with 8% aqueous sodium hydroxide. The acid (58 g.) was boiled for four hours with 300 ml. of absolute alcohol and 55 ml. of sulfuric acid, giving 64.5 g. (87%) of ethyl isoquinoline-4-carboxylate, b.p. 193–195° at 23 mm., m.p. 49°. The ester formed a *picrate*, fine yellow needles from alcohol, m.p. 154–155°.

Anal. Calc'd for $C_{12}H_{11}NO_2 + C_6H_3N_3O_7$: C, 50.2; H, 3.3.
Found: C, 50.4; H, 3.7.

Condensation with ethyl acetate. To a suspension of sodium ethoxide from 2.5 g. of powdered sodium in 25 ml. of dry ether was added 10 g. of ethyl isoquinoline-4-carboxylate and 5 g. of ethyl acetate. The mixture was boiled for thirty hours, then treated with ether and water. From the ether layer was recovered 3.9 g. of ethyl isoquinoline-4-carboxylate, and by adding 6.5 g. of acetic acid to the aqueous layer there was obtained 6.2 g. of crude *ethyl isoquinoline-4,β-ketopropionate*, a thick reddish oil. The keto ester was easily soluble in dil. sulfuric acid and in dil. sodium hydroxide, but not in sodium carbonate solution. It gave a deep red color with alcoholic ferric chloride, and was analyzed in the form of its *picrate*, fine yellow needles from alcohol, m.p. 154–155° (depression when mixed with the picrate of ethyl isoquinoline-4-carboxylate).

Anal. Cal'd for $C_{14}H_{13}NO_3 + C_6H_3N_3O_7$: C, 50.9; H, 3.4.
Found: C, 51.3; H, 3.6.

When 2.7 g. of the keto ester was boiled for thirty minutes with a mixture of 8 ml. of water and 8 ml. of conc'd hydrochloric acid, it was converted into *4-acetoisoquinoline*, a colorless oil that rapidly crystallized after it has been distilled; b.p. 179° at 22 mm., m.p. 72–74°.

Anal. Calc'd for $C_{11}H_9NO$: C, 77.4; H, 5.3.
Found: C, 77.2; H, 5.0.

4-Acetoisoquinoline hydrochloride formed small tan prisms from alcohol-ether that sintered at 185° and melted to a red liquid at 220°.

Anal. Calc'd for $C_{11}H_9NO + HCl$: C, 63.6; H, 4.8.
Found: C, 63.3; H, 5.1.

4-Acetoisoquinoline picrate formed fine bright yellow needles from alcohol, m.p. 180–181°.

Anal. Calc'd for $C_{11}H_9NO + C_6H_3N_3O_7$: C, 51.0; H, 3.0.
Found: C, 51.1; H, 3.3.

Condensation with ethyl 1-benzoylpiperidine-4,β-propionate. A mixture of 3 g. of sodium ethoxide, 15 ml. of dry ether, 5 g. of ethyl isoquinoline-4-carboxylate, and 6 g. of ethyl 1-benzoylpiperidine-4,β-propionate (45) was heated at 65° for twenty-four hours in a sealed tube. The part of the product that was soluble in water was acidified with acetic acid and

extracted with ethyl acetate. Removal of the solvent left 6.3 g. of a brown glassy product, that gave a yellow-brown precipitate with alcoholic ferric chloride. Carbon dioxide was evolved when the glassy product was boiled for twenty minutes with excess 1:1 hydrochloric acid. The resulting solution was basified with excess sodium hydroxide and extracted with ether, giving 2.0 g. of a yellow viscous substance, presumably 4-(1-benzoylpiperidyl-4,β-propionyl)isoquinoline. The substance formed a picrate that sintered at 138° and melted at 148°; despite repeated crystallizations, the *picrate* could not be obtained analytically pure.

Anal. Calc'd for $C_{24}H_{24}N_2O_2 + C_6H_3N_3O_7$: C, 59.9; H, 4.5.
Found: C, 54.4, 55.2; H, 4.3, 4.4.

When 1.9 g. of the viscous partial hydrolysis product was boiled for four hours with 5 ml. of water and 6 ml. of conc'd hydrochloric acid, it gave 0.5 g. of benzoic acid, and 1.05 g. of the *dihydrochloride of 4-(piperidyl-4,β-propionyl)isoquinoline.* Recrystallized from alcohol, this salt formed faintly tan plates that sintered at 240° and melted at 245–248° with decomposition.

Anal. Calc'd for $C_{17}H_{20}N_2O + 2HCl$: C, 59.8; H, 6.5.
Found: C, 59.7; H, 6.1.

The free base was an oil; the *picrate* formed a bright yellow crystalline powder that melted at 175–179° and decomposed a few degrees higher.

Anal. Calc'd for $C_{17}H_{20}N_2O + 2C_6H_3N_3O_7$: C, 47.9; H, 3.6.
Found: C, 48.4; H, 3.9.

SUMMARY

Good yields of condensation products are obtainable from esters of N-heterocyclic acids as a result of the negativity of the nucleus. This negativity is small at the 4-position of the isoquinoline nucleus, and it is shown that ethyl isoquinoline-4-carboxylate undergoes the Claisen condensation comparatively poorly.

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