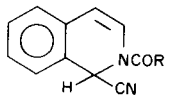
The Isolation and Characterization of Some 1-Alkyl-2-Acyl-1,2-Dihydroisoquinaldonitriles

Harry W. Gibson (1)

Chemicals and Plastics Division, Union Carbide Corporation

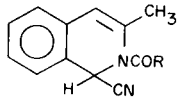
The preparation of 1-alkyl derivatives of 2-acyl-1,2-dihydroisoquinaldonitriles (I) (Reissert compounds) has been well documented (2-9). The reaction has proven to be an efficient route to 1-alkylisoquinolines (4-7,9). These are obtained directly by basic hydrolysis of the 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles (IV). However, in only a few examples has the intermediate IV been isolated and characterized (4-6,8). Pertinent to another investigation (10) we required a series of 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles. Herein we report the preparation, isolation and characterization of a variety of these compounds.

Reissert compounds of types I and II were prepared from the isoquinoline precursors and the acid chlorides by the methylene chloride procedure (11). Many of these were new compounds and the pertinent information for characterization is included in Table I (12). Known compounds agreed with reported data (13) in all respects.



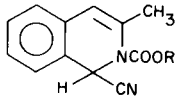
I

a. R = o-C_6H_4Cl
b. R = o-$C_6H_4CH_3$
c. R = p-$C_6H_4CH_3$
d. R = C_6H_5
e. R = CH_3



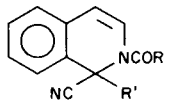
II

a. R = o-C_6H_4Cl
b. R = p-C_6H_4Cl
c. R = CH_3
d. R = $CH(CH_3)_2$
e. R = C_6H_5
f. R = o-$C_6H_4CH_3$
g. R = p-$C_6H_4CH_3$
h. R = α-$C_{10}H_7$
i. R = C_2H_5



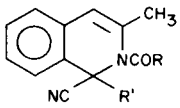
III

a. R = C_2H_5
b. R = $CH_2C_6H_5$



IV

a. R′ = $CH(CH_3)_2$; R = CH_3
b. R′ = $CH(CH_3)_2$; R = C_6H_5
c. R′ = R = $CH(CH_3)_2$
d. R′ = $CH(CH_3)_2$; R = o-C_6H_4Cl
e. R′ = $CH(CH_3)_2$; R = p-C_6H_4Cl
f. R′ = $CH(CH_3)_2$; R = o-$C_6H_4CH_3$
g. R′ = $CH(CH_3)_2$; R = p-$C_6H_4CH_3$
h. R′ = $CH_2CH(CH_3)_2$; R = CH_3
i. R′ = $CH_2CH(CH_3)_2$; R = C_6H_5
j. R′ = $CH_2CH(CH_3)_2$; R = o-$C_6H_4CH_3$
k. R′ = $CH_2C_6H_5$; R = CH_3
l. R′ = $CH_2C_6H_5$; R = C_6H_5
m. R′ = $CH_2C_6H_5$; R = o-$C_6H_4CH_3$
n. R′ = CH_2CH_3; R = CH_3
o. R′ = CH_2CH_3; R = C_6H_5
p. R′ = R = CH_3
q. R′ = $CH(C_2H_5)COOC_2H_5$; R = C_6H_5



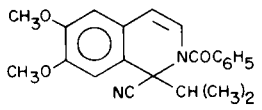
V

a. R′ = $CH(CH_3)_2$; R = CH_3
b. R′ = $CH(CH_3)_2$; R = C_6H_5
c. R′ = R = $CH(CH_3)_2$
d. R′ = $CH(CH_3)_2$; R = o-C_6H_4Cl
e. R′ = $CH(CH_3)_2$; R = o-$C_6H_4CH_3$
f. R′ = $CH(CH_3)_2$; R = α-$C_{10}H_7$
g. R′ = $CH_2CH(CH_3)_2$; R = α-$C_{10}H_7$
h. R′ = $CH_2CH(CH_3)_2$; R = C_6H_5
i. R′ = $CH_2CH(CH_3)_2$; R = o-$C_6H_4CH_3$
j. R′ = $CH(CH_3)_2$; R = p-C_6H_4Cl
k. R′ = $CH(CH_3)_2$; R = p-$C_6H_4CH_3$

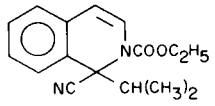
Preparation of compounds of structures IV and V was accomplished by condensation of the appropriate Reissert compound I or II with the required alkyl halide using sodium hydride as base and dimethylformamide as solvent (15). Table II gives the yield, melting point and elemental analyses for new compounds prepared in this manner. Compounds VI and VII were similarly prepared from the corresponding Reissert compounds (16,17).

Some features of these syntheses are noteworthy in that they have not heretofore been observed. It can be seen from Table II that the yields of 1-alkyl-2-acyl-3-methyl-1,2-dihydroisoquinaldonitriles (V) are much lower than those in the parent series (IV). In most cases a second product (VIII) was isolated from the reactions leading to V. Compounds VIIIa-d (see Table III) were produced in excellent yields in the presence of two equivalents of the alkyl halide through the known base catalyzed rearrangement of Reissert compounds (2-4). The desired compounds V were obtained by use of large excesses of the alkyl halides, followed by extensive recrystallization or column chromatography. In some cases (Vh-k) it was not possible to isolate the desired compounds.

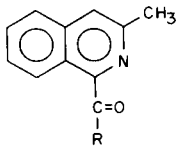
This increased propensity for rearrangement relative to condensation with the alkyl halide must be a reflection of



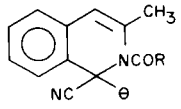
VI



VII



VIII



IX

a. R = C_6H_5
b. R = p-C_6H_4Cl
c. R = o-$C_6H_4CH_3$
d. R = α-$C_{10}H_7$

the decreased stability of the Reissert anions IX. This instability can only be due to the methyl group since the anions of parent compounds I do not rearrange to a detectable extent in the presence of an alkyl halide (4). The methyl group exerts an electron releasing inductive effect which would destabilize the anion IX relative to that derived from I. In addition it is possible that steric interaction of the methyl group and the amide group would be a contributing factor (19).

The nature of the acyl group also effects the tendency for rearrangement, *i.e.*, determines the stability of the anion. It has been found during this investigation that compound Ib will not rearrange at room temperature in the presence of sodium hydride and dimethylformamide while Id does so readily (4). In addition, while alkylation of IIe was difficult to achieve in preference to rearrangement, IIf was fairly readily alkylated. In the proposed mechanism (20) for rearrangement an aziridinyl type intermediate forms as a result of intramolecular nucleophilic attack of the carbanionic center on the carbonyl function. Therefore, to the extent that groups attached to the carbonyl group decrease (or increase) its electrophilicity the rearrangement will be retarded (or accelerated). Electron releasing groups such as methyl on the *N*-benzoyl function would thus be expected to retard rearrangement, as observed, relative to hydrogen, while electron withdrawing groups should accelerate rearrangement. The rearrangement of the chloro substituted compound IIb to VIIIb in 93% yield in the presence of eight equivalents of isopropyl iodide dramatically illustrates the kinetic ramifications of this latter effect!

The second anomaly occurs in the syntheses of compounds IV and V in which R = alkyl. Using an equivalent or more of sodium hydride to generate the required anion does not give rise to the desired compound (19). In order to generate IV and V somewhat less than an equivalent of base must be employed.

TABLE I

Reissert Compounds (a)

Compound	Yield %	M.p.	Formula	Analysis Calculated C	H	N	Found C	H	N
Ia	26	175.5-177.5 (b)	$C_{17}H_{11}N_2ClO$	69.27	3.76	9.51	69.22	3.74	9.53
Ib	87	168.5-169.5	$C_{18}H_{14}N_2O$	78.81	5.14	10.22	78.88	5.18	10.18
Ic	62	127.5-128.5	$C_{18}H_{14}N_2O$	78.81	5.14	10.22	78.85	5.17	10.23
IIa	64	173.0-174.5 (c)	$C_{18}H_{13}N_2ClO$	70.02	4.24	9.08	69.86	4.20	9.09
IIb	68	122.5-124.5 (c)	$C_{18}H_{13}N_2ClO$	70.02	4.24	9.08	69.98	4.20	9.12
IIc	70	99.5-100.5	$C_{13}H_{12}N_2O$	73.56	5.70	13.20	73.46	5.82	13.03
IId	83	104.5-107.5 (c)	$C_{15}H_{16}N_2O$	74.97	6.71	11.67	74.86	6.72	11.70
IIe	77	139.0-140.0 (d)	$C_{18}H_{14}N_2O$	78.81	5.14	10.22	78.73	5.05	10.19
IIf	67	145.0-146.0	$C_{19}H_{16}N_2O$	79.14	5.59	9.72	79.12	5.52	9.75
IIg	66	128.0-129.5	$C_{19}H_{16}N_2O$	79.14	5.59	9.72	79.17	5.61	9.69
IIh	85	198.0-199.5 (b)	$C_{22}H_{16}N_2O$	81.46	4.97	8.64	81.53	5.05	8.71
IIi	81	84.5- 86.0	$C_{14}H_{14}N_2O$	74.31	6.24	12.38	74.24	6.17	12.33
IIIa	36	46.5- 49.5 (e)	$C_{14}H_{14}N_2O_2$	69.40	5.82	11.57	69.48	5.79	11.63
IIIb	55	72.5- 74.5 (c)	$C_{19}H_{16}N_2O_2$	74.98	5.30	9.21	74.86	5.26	9.12

(a) Recrystallized from ethanol unless otherwise noted. (b) Recrystallized from acetic acid. (c) Recrystallized from ethyl acetate-hexane. (d) Reported (14) m.p. 127-128. (e) Recrystallized from hexane.

TABLE II

1-Alkyl-2-acyl-1,2-dihydroisoquinaldonitriles and Analogs (a)

Compound	X of R'X	Yield %	M.p.	Formula	Analysis Calculated C	H	N	Found C	H	N
IVa	I	81	121.5-122.0	$C_{15}H_{16}N_2O$	74.97	6.71	11.67	74.6	6.61	11.5
IVb	Br	83	131.0-132.5 (b,c)							
IVc	I	100	94.0- 95.0	$C_{17}H_{29}N_2O$	76.08	7.51	10.44	76.27	7.44	10.42
IVd	I	95	113.0-117.0	$C_{20}H_{17}N_2ClO$	71.31	5.09	8.32	71.03	5.06	8.41
IVe	I	78	134.5-135.5	$C_{20}H_{17}N_2ClO$	71.31	5.09	8.32	71.08	5.11	8.40
IVf	Br	73	121.5-123.0	$C_{21}H_{20}N_2O$	79.72	6.37	8.86	79.7	6.42	8.7
IVg	I	90	145.5-146.5	$C_{21}H_{20}N_2O$	79.72	6.37	8.86	79.90	6.49	8.83
IVh	I	74	93.0- 94.0	$C_{16}H_{18}N_2O$	75.56	7.13	11.02	75.5	7.15	10.9
IVi	I	79	84.0- 85.5 (d)	$C_{21}H_{20}N_2O$	79.72	6.37	8.86	80.03	6.40	8.70
IVj	I	81	138.0-139.5	$C_{22}H_{22}N_2O$	79.96	6.71	8.48	79.9	6.74	8.4
IVk	Cl	83	136.0-137.5	$C_{19}H_{16}N_2O$	79.14	5.59	9.72	78.8	5.67	9.5
IVl	Cl	83	123.5-125.0 (b,e)	$C_{24}H_{18}N_2O$	82.26	5.18	8.00	81.78	5.14	7.67
IVm	Cl	65	150.5-152.5	$C_{25}H_{20}N_2O$	82.39	5.53	7.69	82.79	5.60	7.69
IVn	Br	62	115.0-116.0	$C_{14}H_{14}N_2O$	74.31	6.24	12.38	73.98	6.24	12.42
IVo	Br	94	108.5-110.5 (b,f)	$C_{19}H_{16}N_2O$	79.14	5.59	9.72	78.94	5.50	9.74
IVp	I	19	95.0- 96.5	$C_{13}H_{12}N_2O$	73.56	5.70	13.20	73.61	5.71	13.29
IVq	Br	86	160.0-161.0	$C_{23}H_{22}N_2O$	73.77	5.92	7.49	73.61	5.92	7.53
Va	I	67	114.0-114.5	$C_{16}H_{18}N_2O$	75.56	7.13	11.02	75.59	7.20	11.00
Vb	I	15	146.0-147.0	$C_{21}H_{20}N_2O$	79.72	6.37	8.86	79.76	6.41	8.81
Vc	I	36	123.5-124.5	$C_{18}H_{22}N_2O$	76.56	7.86	9.92	76.90	7.83	9.84
Vd	I	47	180.0-180.5	$C_{21}H_{19}N_2ClO$	71.89	5.46	7.99	71.90	5.42	8.02
Ve	I	70	183.0-184.0	$C_{22}H_{22}N_2O$	79.96	6.71	8.48	80.05	6.61	8.63
Vf	I	34	200.0-202.0	$C_{25}H_{22}N_2O$	81.94	6.05	7.65	82.35	6.16	7.60
Vg	I	10	155.0-157.0	$C_{26}H_{24}N_2O$	82.07	6.36	7.37	81.84	6.36	7.39
VI	I	83	203.0-204.0 (b)	$C_{22}H_{22}N_2O_3$	72.90	6.12	7.73	73.19	6.17	7.74
VII	I	71	66.0- 67.5 (d)	$C_{16}H_{18}N_2O_2$	71.09	6.71	10.37	71.39	6.52	10.35

(a) Recrystallized from ethyl acetate-hexane unless otherwise specified. (b) Recrystallized from ethanol. (c) Reported (7) m.p. 128-130. (d) Recrystallized from hexane. (e) Reported as a gum (4,18) and solid,, m.p. 129° (8). (f) Reported (8) m.p. 103°.

TABLE III

1-Aroyl-3-methylisoquinolines (a)

Compound	Alkyl Halide Present (Equiv.)	Yield %	M.p.	Formula	Analysis Calculated C	H	N	Found C	H	N
VIIIa	$(CH_3)_2CHI$ (2)	89	102.5-103.0	$C_{17}H_{13}NO$	82.57	5.30	5.67	82.99	5.42	5.38
VIIIb	$(CH_3)_2CHI$ (8)	93	116.5-117.5	$C_{17}H_{12}ClNO$	72.47	4.30	4.97	72.33	4.29	4.80
VIIIc	$(CH_3)_2CHCH_2I$ (1)	100	104.5-105.0	$C_{18}H_{15}NO$	82.73	5.79	5.36	82.83	5.80	5.32
VIIId	$(CH_3)_2CHI$ (2)	77	140.0-140.5 (b)	$C_{21}H_{15}NO$	84.82	5.09	4.71	85.05	5.21	4.60

(a) Recrystallized from hexane unless otherwise noted. (b) Recrystallized from ethyl acetate-hexane.

EXPERIMENTAL

Analyses were performed by the Union Carbide analytical staff and (mostly) by Spang Microanalytical Laboratories, Ann Arbor, Michigan. Melting points were taken in capillaries in a Thomas-Hoover apparatus and are corrected.

2-Acyl-1,2-dihydroisoquinaldonitriles (Reissert Compounds) (I-II).

These were prepared by the methylene chloride method (11). New compounds are listed in Table I.

1-Alkyl-2-acyl-1,2-dihydroisoquinaldonitriles (IV-VII).

Reaction of the Reissert compounds with sodium hydride and alkyl halides by the method of Popp and Wefer (4) led to the new compounds given in Table II. Isopropyl iodide, ethyl iodide and methyl iodide were generally used in one-fold excess. The less volatile halides, isobutyl iodide, benzyl chloride and ethyl α-bromobutyrate, were employed in slight excess generally. For the preparation of Vc a three-fold excess of halide was used; for Vb, Vd-g a seven-fold excess was employed. Purification of Vg was accomplished using chromatography on neutral alumina with successive elution by benzene-methylene chloride, ether and methanol-ether mixtures. Compound VI was also purified in this manner by elution with benzene-carbon tetrachloride, benzene, benzene-methylene chloride, methylene chloride-ether and ether. For the preparation of *N*-acetyl compounds IVa, IVh, IVk, IVn, IVp, and Va only 0.75 equivalent of sodium hydride per equivalent of Reissert compound was employed.

1-Aroyl-3-methylisoquinolines (VIII).

The preparation of these ketones in the presence of excess alkyl halide was carried out exactly as the formation of the 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles (4). New compounds are listed in Table III.

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