SYNTHESIS OF 3-ISOQUINOLONES

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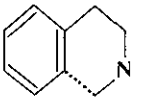
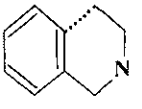
Treatment of N-benzyl-diethoxyacetamides and N-alkyl-N-benzyl-diethoxyacetamides with sulfuric acid afforded the corresponding 3-isoquinolinols and 2-alkyl-3-isoquinolones, respectively. This reaction is regarded as a kind of Pomeranz-Fritsch synthesis.

A number of 3-isoquinolinol derivatives have been shown to be active in the central nervous system.[1] Extensive studies on lactam-lactim tautomerism of 3-isoquinolinols have been reported; however, none of the various previously known methods for the synthesis of 3-isoquinolinol are satisfactory for the reasons that yields are very low and starting materials are not easily accessible.[2,3,4,5]

It is well known that the two most general types of isoquinoline ring formation are types 1 and 2 shown below.



type 1

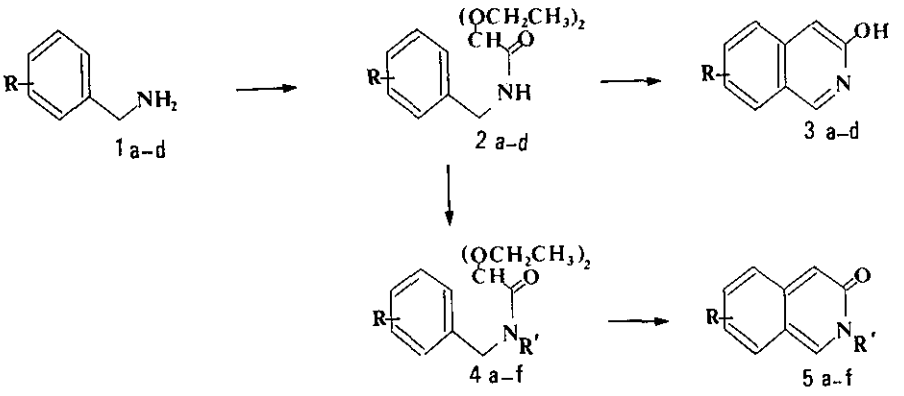


type 2

N-Formyl-2-phenylacetamide, which was formed by the condensation reaction of phenylacetyl chloride with formamide, was treated with mineral acid to give 3-isoquinolinol in moderate yield.[6] This method is an example of type-1 isoquinoline ring formation.

This paper describes a new convenient synthesis corresponding to type 2 (Pomeranz-Fritsch synthesis) for 3-isoquinolinols

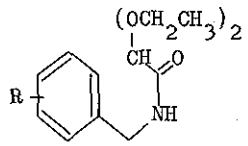
and 2-alkyl-3-isoquinolones. The authors investigated an isoquinoline synthesis in which the intermediate N-benzyl-diethoxyacetamides (2a-d) and N-alkyl-N-benzyl-diethoxyacetamides (4a-f) were cyclized under mild conditions to afford 3-isoquinolinols and 2-alkyl-3-isoquinolones, respectively.



The intermediates (2a-d) in Table 1 were readily prepared in good yields by acylation of benzylamines (1a-d) which diethoxyacetyl chloride, which was obtained from sodium diethoxyacetate and thionyl chloride. The mass spectra of 2a-d exhibited no parent peak or only a weak one, with the prominent peaks occurring at m/e 103 and 75, corresponding to $C_5H_{11}O_2^+$ and $C_3H_7O_2^+$ due to loss of C_2H_4. In the NMR spectra the benzylic methylene proton signals of 2a-d were observed as a doublet with the coupling constant of 6 Hz. On addition of a trace of D_2O, the doublet turned into a singlet.

Successive treatment of 2a-d with sulfuric acid at room temperature afforded the 3-isoquinolinols (3a-d) listed in Table 2. Under the above condition, 2c gave rise to an intractable mixture. The mass spectra of 3a-d showed a prominent M^+-28 peak due to loss of CO. In the spectrum of 3a other significant peaks, corresponding to $C_7H_6^+$ and $C_7H_5^+$, were possibly formed by further loss of HCN and H. 6-Methyl-3-isoquinolinol (3b) had one more

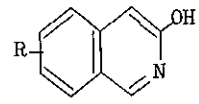
Table 1. Physical and Analytical Data of 2



Compd. No.	R	Yield %	bp °C/mmHg Oil bath temp.	Formula	Analysis % Calcd. (Found) C	H	N	Cl
2a	H	76	140/0.1	$C_{13}H_{19}NO_3$	65.80 (65.89)	8.07 (8.19)	5.90 (6.01)	
2b	4-CH_3	68	140/0.1	$C_{14}H_{21}NO_3$	66.90 (66.74)	8.42 (8.50)	5.57 (5.50)	
2c	3-OCH_3	41	165/0.2	$C_{14}H_{21}NO_4$	62.90 (62.56)	7.92 (7.82)	5.24 (4.94)	
2d	2-Cl	60	155/0.1	$C_{13}H_{18}ClNO_3$	57.45 (57.51)	6.68 (6.62)	5.16 (5.06)	13.05 (13.07)

Compd. No.	IR cm^{-1} in $CHCl_3$	NMR (δ, ppm) in $CDCl_3$ $\underline{CH_3}CH_2O$	$CH_3\underline{CH_2}O$	$Ar\underline{CH_2}N$	$(EtO)_2\underline{CH}$	$\underline{NH}$	Mass m/e
2a	3460 1696	1.23(t)	3.68(q)	4.50(d)	4.88	6.90	237(M^+), 103, 91, 75
2b	3420 1682	1.22(t)	3.68(q)	4.45(d)	4.87	6.90	251(M^+), 149, 105, 103, 75
2c	3430 1685	1.22(t)	3.68(q)	4.47(d)	4.83	7.00	267(M^+), 121, 103, 75
2d	3430 1688	1.23(t)	3.68(q)	4.60(d)	4.85	7.10	273(M^++2), 271(M^+), 125, 103, 75

Table 2. Physical and Analytical Data of 3

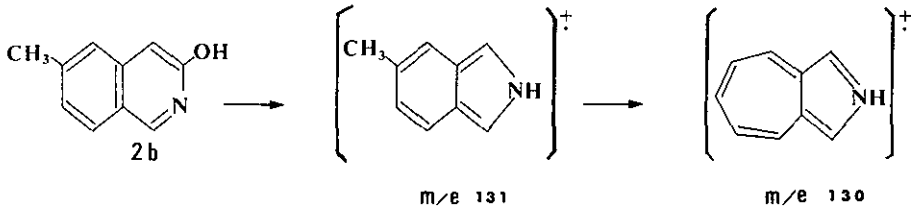


Compd. No.	R	Yield %	mp °C	Formula	Analysis % Calcd. (Found) C	H	N	Cl
3a	H	60	200 (lit* 195-196)					
3b	6-CH_3	32	253 (decomp.)	$C_{10}H_9NO$	75.45 (75.20)	5.70 (5.70)	8.80 (8.63)	
3c	7-OCH_3	-						
3d	8-Cl	38	228 (decomp.)	C_9H_6ClNO	60.19 (59.93)	3.37 (3.31)	7.80 (7.42)	19.74 (19.96)

Compd. No.	IR cm^{-1} KBr	NMR (δ, ppm) in d_6-DMSO C_1-H	C_4-H	Mass m/e
3a	3430, 1635	8.93	6.95	145(M^+), 117(M^+-28, base), 90, 89
3b	3440, 1635	8.85	6.82	159(M^+), 131(M^+-28, base), 130, 103, 77
3c				
3d	3430, 1638	9.18	7.05	181(M^++2), 178(M^+), 153, 151(M^+-28, base) 116, 89

* J. H. Boyer and L. T. Wolford, J. Org. Chem., 1959, 21, 1297.

significant peak at m/e 130 which corresponded to loss of one mass unit from the M^+-28 peak, this ion resulting from the incorporation of the 6-methyl group into the benzene ring.



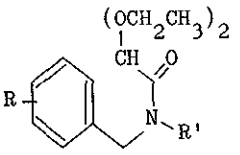
The mass spectrum of 8-chloro-3-isoquinolinol (3d) exhibited a base peak of M^+-28 and a prominent peak at m/e 116 ($C_8H_6N^+$) due to loss of Cl from the base peak.

The alkylation of 2a-d was performed at room temperature with 1.5 equivalents of NaH and alkyl halide in DMSO to give N-alkyl-N-benzyl-diethoxyacetamide (4a-f) as shown in Table 3. The mass spectra of 4a-f had no parent peak or only a weak one with prominent peaks occurring at m/e 103 and m/e 75, corresponding to $C_5H_{11}O_2^+$ and $C_3H_7O_2^+$ in a similar manner to 2a-d. In the NMR spectrum the benzylic methylene protons of 4a-f resonated as two separate singlets as a result of the restricted rotation. The NMR spectra of N-ethyl compounds (4b and 4f) also exhibited two singlets due to the methine proton attached to the acetal carbon.

2-Alkyl-3-isoquinolones (5a-f) except 5e were formed in good yield by the cyclization of 4a-f with conc. H_2SO_4 as listed in Table 4. NMR, IR and mass spectra of 5a-f were taken immediately after chromatographic separation, and showed only slight contamination.

The inspection of NMR spectra showed the products to be pure, but elementary analysis of them except 5d and 5f gave low carbon and nitrogen values, probably owing to autoxidation. 2-Methyl-3-isoquinolone has been previously described as being unstable[2] and deteriorating rapidly.[3] Surprisingly the two compounds, 5d and 5f, were stable enough to allow recrystallization

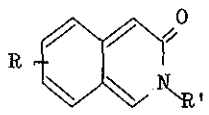
Table 3. Physical and Analytical Data of 4



Compd. No.	R	R'	Yield %	bp °C/mmHg Oil bath temp.	Formula	Analysis % Calcd. (Found) C	H	N	Cl
4a	H	CH_3	88	135/0.1	$C_{14}H_{21}NO_3$	66.90 (66.78)	8.42 (8.49)	5.57 (5.37)	
4b	H	C_2H_5	94	140/0.1	$C_{15}H_{23}NO_3$	67.92 (67.69)	8.68 (8.88)	5.28 (5.28)	
4c	H	$CH_2C_6H_5$	91	160/0.1	$C_{20}H_{25}NO_3$	73.36 (73.57)	7.70 (7.82)	4.28 (4.07)	
4d	4-CH_3	CH_3	83	140/0.1	$C_{15}H_{23}NO_3$	67.92 (67.73)	8.68 (8.72)	5.28 (5.27)	
4e	3-OCH_3	CH_3	98	140/0.01	$C_{15}H_{23}NO_4$	64.03 (63.91)	8.24 (8.29)	4.98 (4.79)	
4f	2-Cl	C_2H_5	99	160/0.1	$C_{15}H_{22}ClNO_3$	60.09 (60.37)	7.40 (7.52)	4.67 (4.47)	11.82 (11.60)

Compd. No.	IR cm^{-1} in $CHCl_3$	NMR (δ, ppm) in $CDCl_3$ CH_3CH_2O	CH_3CH_2O	$ArCH_2N$	$(EtO)_2CH$	NR'	Mass m/e
4a	1645	1.20(t) 1.23(t)	3.68(q) 3.73(q)	4.60 4.80	5.07	2.83 3.06	251(M^+), 103, 91, 75
4b	1640	1.13(t) 1.23(t)	3.1-3.7 (4H,m)	4.62 4.78	5.02 5.07	1.13(3H) 3.4-4.0(2H)	265(M^+), 103, 91, 75
4c	1642	1.18(t)	3.70(q) 3.75(q)	4.70	5.12	4.52(s) 7.30(5H)	327(M^+), 103, 91, 75
4d	1645	1.20(t) 1.23(t)	3.67(q) 3.70(q)	4.55 4.73	5.05	2.82 3.03	265(M^+), 165, 103, 75
4e	1650	1.20(t) 1.23(t)	3.69(q) 3.72(q)	4.58 4.77	5.07	2.83 3.06	281(M^+), 121, 103, 91
4f	1645	1.14(t) 1.27(t)	3.1-3.7 (4H,m)	4.73 4.87	4.95 5.07	1.12(3H) 3.4-4.0(2H)	301(M^++2), 299(M^+), 125, 103, 75

Table 4. Physical and Analytical Data of 5



5a-f

Compd. No.	R	R'	Yield	IR cm^{-1} in $CHCl_3$	NMR (δ, ppm) in $CDCl_3$ C_1-H	C_4-H	N-R'	Mass m/e
5a	H	CH_3	87	1658	8.19	6.77	3.85(3H)	159(M^+), 131(base)
5b	H	C_2H_5	83	1658	8.23	6.70	1.43(3H) 4.28(2H)	173(M^+, base), 145, 117
5c	H	$CH_2C_6H_5$	83	1660	8.13	6.77	5.43(2H) 7.35(5H)	235(M^+, base), 91
5d	6-CH_3	CH_3	84	1662	8.11	6.62	3.78(3H)	173(M^+, base), 145, 144
5e	7-OCH_3	CH_3	16	1662	8.00	6.70	3.78(3H)	189(M^+, base), 174, 161, 146, 118
5f	8-Cl	C_2H_5	90	1658	8.52	6.78	1.50(3H) 4.35(2H)	209(M^++2), 207(M^+, base), 181, 179, 153, 151

from benzene. Although it was expected that the cyclization of 4e could take place at the positions ortho and para to the methoxyl group, only one isomer, 7-methoxy-2-methyl-3-isoquinolone (5e), was isolated in low yield. The structure of 5e was confirmed by the NMR spectrum which revealed the five aromatic protons [6.60 (d, J=2, H_8), 6.70 (s, H_4), 7.03 (d,d, J=2, J=9, H_6), 7.25 (d, J=9, H_5) and 8.00 (s, H_1)]. The mass spectrum of the 2-alkyl-3-isoquinolone compounds showed a simple fragmentation pattern with only one prominent peak (M^+-28). The 6-methyl derivative had an additional peak at M^+-29 which was formed by rearrangement to the N-methyl-aza-azulenium ion with loss of one hydrogen. The mass spectra of 2-ethyl-3-isoquinolone (5b) exhibited a M^+-28 peak due

to loss of CO and another strong peak corresponding to $C_8H_7N^+$ which was formed by further loss of C_2H_4. The fragmentation of 5e involves a combination of the loss of a methyl, and one or two carbonyl groups. The mass spectrum of 8-chloro-2-ethyl-3-isoquinolone exhibited the molecular ion as a base peak, a M^+-28 peak and a prominent peak due to loss of C_2H_4 to give $C_8H_6ClN^+$. Proton signals at the C1 and C4 position of 3-isoquinolones (5a-f) appeared as singlets at 8.0-8.5 and 6.6-6.8 ppm, respectively.

Experimental

General Procedure

N-Benzyl-diethoxyacetamide (2a-d)

To a solution of sodium diethoxyacetate (20 g) in dry ether (80 ml) was added thionyl chloride (11.9 g) under stirring for 10 min at 10°. The reaction mixture was refluxed for 30 min and after cooling, poured into a solution of benzylamine (1, 0.1 mol) in benzene (50 ml) and pyridine (30 ml) at 20-30° with vigorous stirring. After refluxing for 30 min, the reaction mixture was poured into ice-water and extracted with benzene. The extracts were washed successively with 2% HCl and water. Evaporation of the solvent gave the crude product which was chromatographed on silica gel using AcOEt-benzene (1:9) as an eluent.

3-Isoquinolinol (3a-d)

N-Benzyl-diethoxyacetamide (2, 10 mmol) was carefully dissolved in conc. H_2SO_4 (16 ml) under stirring and cooling at 10-20°. The reaction mixture was left to stand for 10 hr at room temperature and poured into ice-water and filtered. The filtrate was neutralized with 10% NH_4OH and the resulting yellow precipitate was filtered off and dried. Recrystallization from EtOH gave yellow needles.

N-Alkyl-N-benzyl-diethoxyacetamide (4a-f)

To a mixture of NaH (50% in mineral oil, 0.72 g) and DMSO (20 ml) was added N-benzyl-diethoxyacetamide (2, 10 mmol) in an atmosphere of nitrogen. After evolution of hydrogen ceased, alkyl halide (methyl iodide, ethyl iodide or benzyl bromide) was added to the mixture under cooling by water. After stirring for 30 min at room temperature, the reaction mixture was poured into ice-water and extracted with benzene. Evaporation of the solvent gave the crude product, which was purified on silica gel, eluting with benzene.

2-Alkyl-3-isoquinolone (5a-f)

N-Alkyl-N-benzyl-diethoxyacetamide (4, 10 mmol) was dissolved in conc. H_2SO_4 (20 ml) under stirring and cooling at 10-20°. The reaction mixture was left to stand for 4 hr at room temperature and poured into ice-water. After neutralization with 10% NH_4OH, the mixture was extracted with $CHCl_3$. The extracts were chromatographed on neutral alumina with $CHCl_3$ as eluent. The solvent was evaporated under reduced pressure at 30-35°. 5d and 5f were recrystallized from benzene to give yellow needles.

5b mp 175-177° (decomp.) Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.19; H, 6.25; N, 7.86.

5d mp 76-86° Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75; Cl, 17.07. Found: C, 63.30; H, 4.58; N, 6.51; Cl, 16.72.

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