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Preparation and Properties of *N*-Monoalkylated Imidic Esters

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Imidic esters were prepared by the action of triethyloxonium tetrafluoroborate or dimethylsulphate on secondary amides or by the action of alcohols on nitrilium salts. The compounds hydrolyze easily in water, have basic properties and form crystalline tetrafluoroborates. Salt formation gives rise to two isomeric products. The synthetic utility of the functional group was examined. A mild deacetylation method was worked out. Tetrazoles were formed by the action of hydrazoic acid on nitrilium salts. Acylation of imidic esters leads to 1-alkoxy-1-acylamino-1-alkenes.

Members of the aromatic series are well known and used synthetically for the preparation of diarylamines (Chapman rearrangement [1]). Apart from cyclic imidic esters,[2] few aliphatic derivatives have been described due to their sensitivity to hydrolytic cleavage. Scattered information on preparations and properties is found in the literature.[1,3–15] This work presents properties and preparative methods together with an investigation of the synthetic utility of the functional group.

Preparation of imidates. Method A. Addition of alcohols to nitrilium salts, prepared from nitriles and triethyloxonium tetrafluoroborate,[16] gave crystalline salts of imidic esters, which upon treatment with base afforded the free imidic esters, eqn. (1).

$$R-C\equiv\overset{+}{N}-C_2H_5 \xrightarrow{R'OH} R-\underset{\underset{OR'}{|}}{C}=\overset{+}{N}HC_2H_5 \xrightarrow{OH^-} R-\underset{\underset{OR'}{|}}{C}=NC_2H_5 \qquad (1)$$

Method B. Secondary amides are *O*-alkylated in high yields by triethyloxonium tetrafluoroborate in methylene chloride, eqn. (2).

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$$R-C(=O)-NHR' \xrightarrow{(C_2H_5)_3O^+} R-C(-OC_2H_5)=+NHR' \qquad (2)$$

The neutralization stage is critical and low yields are experienced because of hydrolytic cleavage. *N*-Phenylcaproamide, *N*-ethyl and *N*-phenyl-phenylacetamide, benzanilide, and *N*-ethylbenzamide were *O*-alkylated quantitatively, as judged by the IR spectra of the crude products; but on neutralization the starting material was isolated as the main product. In general, higher yields of imidic esters were obtained when the crude product, freed from solvent, was added with cooling to the aqueous base.

Method C. O-Methylation can be accomplished by heating the amide for several hours with dimethyl sulphate, which is less active than the ethyloxonium salt. Simple aliphatic amides, acetanilide, *p*-methoxyacetanilide (reacts rapidly), benzamide, were alkylated whereas *p*-nitroacetanilide and benzanilide were not attacked. Thus a high electron density on the oxygen is favourable for the reaction.

Properties. The amidates are colourless basic liquids with an amine-like odour. They give crystalline deliquescent tetrafluoroborates and hydrolyze quickly according to route 3a and/or b in acidic solution, but are fairly stable in alkaline solution.

$$R-C(=NR')-OC_2H_5 \rightarrow R-C(=O)-OC_2H_5 + R'NH_2 \qquad (3a)$$

$$R-C(=NR')-OC_2H_5 \rightarrow R-C(=O)-NHR' + C_2H_5OH \qquad (3b)$$

The polarity of the amidates is lower than that of the amides, which is evident from the difference in boiling points of the isomeric compounds I and II.

$C_2H_5-C(=O)-N(C_2H_5)_2$ I 191°/760

$C_2H_5-C(=NC_2H_5)-OC_2H_5$ II 126–127°/760

According to the IUPAC nomenclature II is to be named ethyl *N*-(ethyl) propanimidate.

Spectral data. The imidates have a strong absorption band around 1666 cm^{-1} in the IR range, with an intensity of approx. 500. *N*- or *C*-arylation and salt formation affect the position and intensity only slightly. Tables 1 and 2. The salts show a second band around 1535 cm^{-1}, with less than half the intensity of the former absorption. Our findings have bearings on the interpretation of the origin of the amide bands I and II. The secondary amides

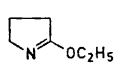
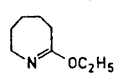
exhibit a strong carbonyl absorption near 1650 cm^{-1} and a second band in the region of 1550 cm^{-1}. Since the amide I band (N—C=O) and the imidate band (N=C—O) fall in the same position, the assignment of the absorption at 1550 cm^{-1} to a C=N stretching motion of double bond character is irrelevant. The view that the second band originates from N—H deformation motions [17] is strongly supported.

In the NMR spectra, the OCH_3 group of the imidic function is found at $\delta=3.63$ ($CDCl_3$). II gave the following data ($CDCl_3$): $\delta=4.06$, O—CH_2—, q; $\delta=3.28$, N—CH_2—, q; $\delta=2.26$, C—CH_2, q; $\delta=1.23$, OCH_2CH_3, t; $\delta=1.13$, NCH_2CH_3, t; $\delta=1.11$, CCH_2CH_3, t. The coupling constant of the ethyl protons is 7.0 cps. In the salts the positions of the protons around the functional group are shifted to lower field, HBF_4 salt of II: $\delta=4.61$, O—CH_2—, q; $\delta=3.45$, N—CH_2—, quint; $\delta=2.84$, C—CH_2, q. The N—CH_2 protons couple both with the NH and the CH_3 group and appear as a quintet.

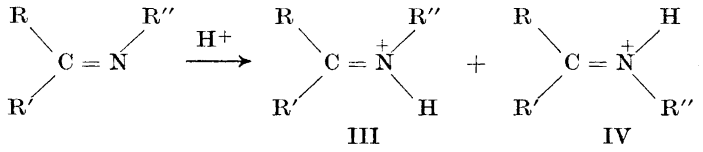
The aliphatic imidates and salts show only end absorption in the UV region, $\varepsilon_{230} < 100$.

Cis-trans isomerism. Salt formation is expected to give two products III and IV.

Table 1. Physical data of imidic esters, R—C(=NR″)—OR′

R	R′	R″	Yield %	B.p. °C/mm Hg	Mol. weight	Method	$\nu_{C=N}$ cm^{-1} $CHCl_3$	ε
C_2H_5	C_2H_5	C_2H_5	25	126—127/760	129.2	B	1667	428
C_2H_5	C_2H_5	C_2H_5	56	127—130/760	129.2	A	1667	447
CH_3	C_2H_5	C_6H_5	65	98—99/14 [a]	163.2	B	1665	655
C_2H_5	C_2H_5	C_6H_5	61	97—98/12	177.2	B	1660	624
CH_3	C_2H_5	n-C_6H_{13}	60	147—148/12	171.3	B	1668	435
CH_3	C_2H_5	C_2H_5	6	113/760	115.2	A	1674	—
CH_3	i-C_3H_7	C_2H_5	37	125/760	129.2	A	1671	409
CH_3	cyclohexyl	C_2H_5	73	92—95/20	169.3	A	1672	—
C_2H_5	CH_3	C_2H_5	32	113—115/760	115.2	A	1672	365
C_2H_5	i-C_3H_7	C_2H_5	59	42—43/19	143.2	A	1668	473
C_2H_5	cyclohexyl	C_2H_5	69	100/19	183.2	A	1667	515
C_2H_5	CH_3	C_3H_7	31	31—33/12	129.2	C	1679	—
CH_3	CH_3	C_6H_5	36	91—92/17 [b]	149.2	C	1666	—
C_6H_5	CH_3	H	37	93—95/12 [c]	135.2	C	1628	—
$C_6H_5CH_2$	CH_3	H	19	100—102/12	149.2	C	1660	—
CH_3	CH_3	*p*-$OCH_3C_6H_4$	52	115—116/10	179.2	C	1665	—
			47	139/760	113.2	B	1645	500
			59	69/14 [d]	141.2	B	1662	416

[a] Lit.[4] 207—208°/760; [b] lit.[5] 81—82°/12; [c] lit.[5] 95—97°/14—15; [d] Benson, R. E. and Cairns, T. L. *J. Am. Chem. Soc.* **70** (1948) 2115: 81—82°/26 mm.

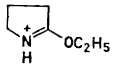
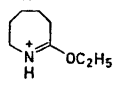


III IV

The NMR spectra of the free bases at room temperature do not reveal the presence of stable isomers, but in some cases isomeric salt pairs are formed, *e.g.* R=CH_3, C_2H_5; R′=C_2H_5, and R″=phenyl. CCH_3 (s) was located at δ=2.07 and 2.70 and OCH_2 (q) at δ=4.43 and 4.70. The values for the *C*-ethyl derivative were: CCH_2 (q) δ=2.35 and 2.99 and OCH_2 (q) δ=4.39 and 4.69 ($CDCl_3$), respectively.

Synthetic utility of imidic esters. Reduction. While this work was in progress, some communications [11,13,14] covering part of our work appeared. It was our intention to test if the esters or salts could be reduced selectively by borohydrides. Preliminary experiments showed, however, that aldehydes were

Table 2. Physical data of imidic ester salts, R−C(OR′)=$\overset{+}{N}$HR″, BF_4^-

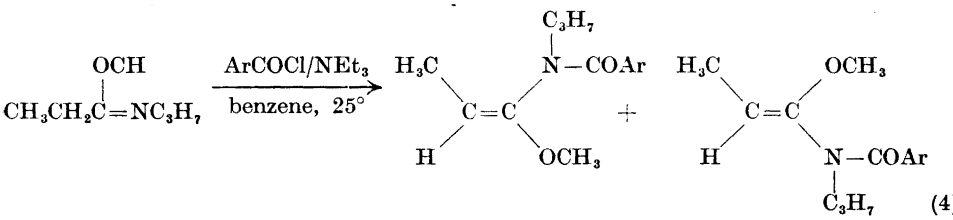
R	R′	R″	Yield %	M.p. °C	Mol. weight	Method	$\nu_{C=N}$ cm^{-1} CH_2Cl_2	ε	ν_{N-H} cm^{-1} CH_2Cl_2
C_2H_5	C_2H_5	C_2H_5	72	104−5	217.0	B	1668	537	1534
CH_3	C_2H_5	C_6H_5	85	157−8	251.0	B	1658	524	1554
C_2H_5	C_2H_5	C_6H_5	87	77−9	263.1	B	1650	381	1549
CH_3	C_2H_5	n-C_6H_{13}	85[a]	oil	259.1	B	1673	475	1543
C_2H_5	C_2H_5	C_2H_5	46	104−5	217.0	A	—	—	—
C_2H_5	CH_3	C_2H_5	60	88−90	203.0	A	1674	443	1532
C_2H_5	i-C_3H_7	C_2H_5	80	116−8	221.0	A	1665	481	1526
C_2H_5	cyclohexyl	C_2H_5	70	90.5−1	269.1	A	1664	503	1526
CH_3	CH_3	C_2H_5	85[a]	oil	187.0	A	—	—	—
CH_3	C_2H_5	C_2H_5	87[a]	oil	203.0	A	—	—	—
CH_3	i-C_3H_7	C_2H_5	92[a]	oil	217.0	A	—	—	—
CH_3	cyclohexyl	C_2H_5	74[a]	oil	255.1	A	—	—	—
C_6H_5	CH_3	C_2H_5	65[a]	oil[c]	275.3	C	1658	—	—
$C_6H_5CH_2$	CH_3	C_2H_5	60[a]	oil[c]	289.3	C	1663	—	—
$C_6H_5CH_2$	CH_3	C_6H_5	20[a]	oil[c]	337.3	C	—	—	—
CH_3	CH_3	C_6H_5	61	77−9[c]	261.3	C	1660	—	—
CH_3	CH_3	$C_6H_4OCH_3$	82	70−2[c]	291.3	C	—	—	—
C_2H_5	CH_3	C_3H_7	62	oil[c]	241.2	C	1655	—	—
			80	48−9.5	201.0	B	1669	863	[b]
			88	61−3	229.0	B	1663	803	1506

[a] Crude yield; [b] missing; [c] dimethyl sulphate salt.

not formed. Borch [13] obtained the same result and showed that reduction with excess sodium borohydride gave amines in good yields.

Hydrolysis. Removal of protecting groups. The hydrolysis proceeds rapidly in a weakly acid medium. The acetyl and propanoyl derivatives are cleaved according to route 3a; thus *N*-deacetylation can be carried out under mild conditions by *O*-ethylation, followed by treatment with water. On the other hand debenzoylation or cleavage of the peptide bond by the same sequence of reactions was not successful.

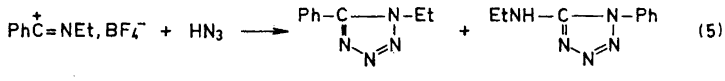
Acylation. The imidic function is not prone to react with carbanions. No reaction was noted between acetyl acetone and *N*-phenyl acetimidate in benzene-pyridine solution. Intramolecular reaction of suitably situated centres has been accomplished.[14] Acylation gave among other products 1-alkoxy-1-acylamino-1-alkenes, eqn. (4), the structure of which was proved by IR and NMR data.



(4)

Pyrolysis. The aliphatic imidates do not undergo Chapman rearrangement nor are olefins formed by elimination. The *O*-cyclohexyl derivative was stable at temperatures below 250°. No *N*-ethylaniline was formed on heating the tetrafluoroborate of ethyl *N*-(ethyl)benzimidate at 180° for 3 hours.

Tetrazoles. Treatment of nitrilium salts with hydrazoic acid in methylene chloride at room temperature gave tetrazoles in fair yields. Both 1-ethyl-5-phenyltetrazole and the rearrangement product 1-phenyl-5-ethylaminotetrazole were isolated from the *N*-ethylbenzonitrilium salt.



(5)

No tetrazoles could be isolated from the reaction of sodium azide with imidic esters in DMSO at 100°.

EXPERIMENTAL

All compounds described gave satisfactory analysis or a correct proton integral of their NMR spectra (Varian A 60-A). The IR spectra were run by a Perkin-Elmer 221 instrument.

Ethyl N-(ethyl)propanimidate and its tetrafluoroborate. Method A. Ethanol (1.0 g) was added to a cooled and stirred solution of the crude nitrilium salt (3.4 g, prepared from propionitril and triethyloxonium tetrafluoroborate [16]) in dry methylene chloride. Half of the solvent was evaporated and the salt was precipitated with ether. It was

crystallized from methylene chloride-ether, m.p. 104–105°, 72 %. The salt liquefies in contact with humid air, but can be kept for months in a refrigerator.

The free ester was obtained by adding the salt (5 g) in portions to chilled and stirred aqueous sodium hydroxide (25 ml, 4 M). The organic layer was dried over sodium sulphate and distilled, b.p. 127–130°/760 mm Hg, 56 %. A further quantity (impure) was obtained by extraction of the water phase with ether.

The *O*-methyl, *O*-isopropyl, *O*-cyclohexyl derivatives and the compounds derived from the acetonitrilium salt [16] were prepared analogously.

The tetrafluoroborate of ethyl N-*(phenyl)acetimidate. Method B.* Acetanilide (15 g), triethyloxonium tetrafluoroborate (20.8 g) was stirred in methylene chloride (120 ml) for 6 h at room temperature. Half of the solvent was evaporated and ether (25 ml) was added. The salt was washed with ether and dried, m.p. 157–158°, 85 %. The salt must be stored in a stoppered bottle in a refrigerator.

Ethyl N-*(phenyl)acetimidate.* The crude reaction mixture (above) was evaporated to dryness and added in portions with cooling and stirring to aqueous sodium hydroxide (55 ml, 4 N). Ether (25 ml) was added and the organic phase was separated, dried and freed from solvent. Distillation *in vacuo* yielded the imidate, b.p. 97–98°/12 mm Hg, 65 %.

Hydrolysis. The tetrafluoroborate of ethyl *N*-(phenyl)acetimidate (2.8 g) was dissolved in water (30 ml). After one hour, aniline was isolated in a yield of 87 %. The solution smelled strongly of ethyl acetate

When the *tetrafluoroborate of ethyl* N-*(ethyl)benzimidate* was hydrolyzed in a similar manner, the amide was recovered as the main product and only small amounts of ester and amine were formed.

Methyl N-*(propyl)propanimidate. N*-Propyl propanamide (11.5 g) and dimethyl sulphate (19 g) were refluxed for 2 h in chloroform (20 ml). The salt was precipitated as an oily mass with ether (125 ml) and washed with an additional quantity of ether (10 ml). The crude yield was 62 %. The salt was added in portions with cooling to sodium hydroxide (25 ml, 5 N) and the organic phase was separated, dried with sodium sulphate and distilled, b.p. 31–33°/12 mm Hg, 31 %.

Acylation. To a solution of methyl *N*-(propyl)propanimidate (3 g) and triethylamine (2.4 g) in ether (75 ml) *p*-NO_2-benzoyl chloride (4.35 g) was added in portions with stirring. After 3 days the triethylamine hydrochloride was filtered off and the ether evaporated. A viscous oil remained (5 g), part of which was chromatographed on silica with chloroform. Two isomeric 1-alkoxy-1-*p*-nitrobenzoylamino-1-propenes were obtained as a partly resolved oily main fraction together with *N*-propyl-*p*-nitrobenzamide, which were analyzed by NMR and IR. One of the isomers gave the following data: IR ($CHCl_3$), 1650 cm^{-1}, C=O; 1528 cm^{-1}, NO_2, NMR ($CDCl_3$), $\delta=7.97$, AB system, 4H; $\delta=4.24$ (q) $J=6.8$ cps, =CH; $\delta=3.62$ (t) $J=6$ cps, $N-CH_2$; $\delta=3.48$ (s) OCH_3; $\delta=2.0-1.3$ (m) NCH_2-CH_2; $\delta=1.32$ (d) $J=6.8$ cps, $=C-CH_3$; $\delta=0.98$ (t) CH_2-CH_3.

Tetrazoles. N-Ethyl-benzonitrilium salt from benzonitril (5.15 g, 50 mmoles) was reacted with hydrazoic acid (50 mmoles) at room temperature in methylene chloride for 6 h. The solvent was evaporated and the oil was poured into water, neutralized with sodium carbonate and extracted once with light petrol ether. Chromatography on silica (chloroform and chloroform/methanol, 5–10 %) gave *1-ethyl-5-phenyltetrazole*, m.p. 116–117°, (lit.[18] 118–119°), 15 % and *1-phenyl-5-ethylaminotetrazole*, m.p. 69–70°, (lit.[19] 70–71°), 18 %.

1,5-Diethyltetrazole was obtained in a yield of 27 % by the action of hydrazoic acid on the *N*-ethyl propionitrilium salt as described above. The crude product was distilled (extraction with petrol ether was omitted), b.p. 138–141°/5 mm Hg, m.p. 31–32 (lit.[20] b.p. 83–85°/0.12 mm Hg).

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REFERENCES

1. Schulenberg, J. W. and Archer, S. *Org. Reactions* **14** (1965) 1.
2. Seeliger, W., Aufderhaar, E., Diepers, W., Feinauer, R., Nehring, R., Thier, W. and Hellmann, H. *Angew. Chem. Intern. Ed.* **5** (1966) 875.
3. Meerwein, H., Borner, P., Fuchs, O., Sasse, H. J., Schrodt, H. and Spille, J. *Chem. Ber.* **89** (1956) 2060.
4. Lander, G. D. *J. Chem. Soc.* **79** (1900) 690; **83** (1903) 406.
5. Bühner, A. *Ann.* **333** (1904) 289.
6. Meerwein, H., Battenberg, E., Gold, H., Pfeil, E. and Willfang, G. *J. prakt. Chem.* **154** (1939) 83.
7. Roberts, R. M. and Hussein, F. A. *J. Am. Chem. Soc.* **82** (1960) 1950.
8. Roberts, R. M., Higgins, Jr., T. D. and Noyes, P. R. *J. Am. Chem. Soc.* **77** (1955) 3801.
9. Roger, R. and Neilson, D. G. *Chem. Rev.* **61** (1961) 179.
10. Bredereck, H., Effenberger, F. and Henseleit, E. *Chem. Ber.* **98** (1965) 2754.
11. Hanessian, S. *Tetrahedron Letters* **1967** 1549.
12. Borrman, D. and Wegler, R. *Chem. Ber.* **100** (1967) 1814.
13. Borch, R. F. *Tetrahedron Letters* **1968** 61.
14. Oishi, T., Ochiai, M., Nagai, M. and Ban, Y. *Tetrahedron Letters* **1968** 492, 497.
15. Weintraub, L., Oles, S. R. and Kalish, N. *J. Org. Chem.* **33** (1968) 1679.
16. Meerwein, H., Laasch, P., Mersch, R. and Spille, J. *Chem. Ber.* **89** (1956) 209.
17. Bellamy, L. J. *The IR Spectra of Complex Molecules*, Methuen and Co., London 1958, p. 216.
18. Finnegan, W. G., Henry, R. A. and Lieber, E. *J. Org. Chem.* **18** (1953) 779.
19. Harbill, E. K., Herbst, R. M., Schreiner, E. C. and Roberts, C. W. *J. Org. Chem.* **15** (1950) 662.
20. Lee, L. A., Crabtree, E. V., Lowe, Jr., J. V., Cziesla, M. J. and Evans, R. *Tetrahedron Letters* **1965** 2885.

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