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ACETYLSALICYLAMIDE
O- TO N-ACETYL MIGRATION[1a]

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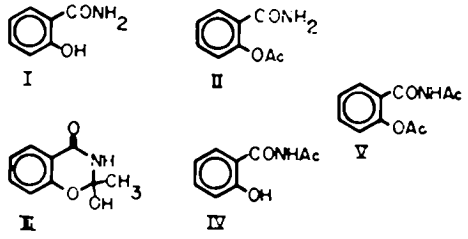
Abstract—O-Acetylsalicylamide rapidly and irreversibly rearranges to the more stable isomer, N-acetylsalicylamide, under a variety of conditions; for example, standing at room temperature in MeOH, EtOH, pyridine or dil aq base; in the solid state below the m.p.; above 100° in acetone. The rearrangement is readily followed by NMR, UV and DTA. The N-acetyl isomer exhibits at least 3 crystalline modifications (120°, 137°, 146°), thus partially explaining the discrepancies in the reported properties of the acetylsalicylamide system.

IN A group of early papers[2,3] it was reported that some attempts to prepare O-acetylsalicylamide (II) from salicylamide (I) gave instead an isomer whose structure was suggested to be either III or IV.[4] The O-acetyl compound could be prepared by reaction of I in the cold with an acetic anhydride–pyridine mixture.[2] However, it proved to be unstable and isomerized in mild base or during melting.[5,6] Both II and its isomer could be converted to V under forcing conditions.[5] All structure assignments for the isomers were based on combustion analyses, cryoscopic molecular weights, m.p. behaviour and the ferric chloride test. The earlier work[2,3] was criticized by von Auwers;[7] replies to his criticism[5,6,8] apparently ended the controversy and structure IV was assigned to the isomer.[5,6]



However, a literature search of the acetylsalicylamide system has uncovered considerable discrepancies in the thermal and chemical behaviour reported by various authors. M.ps. for II have been given from 130–153°[3,5,6,9] and thermal isomerization has been reported to occur considerably below the m.p.[6] Preparations of pure II in

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[2] J McConnan and A Titherley, *J. Chem. Soc.* **89**, 1318 (1906) and Refs cited therein. For additional background, see E. H. Rodd, *Chemistry of Carbon Compounds*, Vol III, Part B, p. 764. Elsevier, Amsterdam (1956)

[3] C. Gerhardt and L. Chiozza, *Liebigs Ann.* **87**, 296 (1853); H. Limpricht, *Ibid.* **99**, 249 (1856).

[4] Benzoylation of I has been claimed to give all three compounds corresponding to structures II, III and IV.[3,5]

[5] A. Titherley and W. L. Hicks, *J. Chem. Soc.* **99**, 866 (1911).

[6] R. Anschütz, H. Aschenberg, H. Kuckertz, F. Krone, K. Riepenkröger and C. Zerbe, *Liebigs Ann.* **442**, 18 (1925).

[7] K. v. Auwers, *Ber. Dtsch. Chem. Ges.* **40**, 3507 (1907); **38**, 3526 (1905).

[8] A. Titherley, *Proc. Chem. Soc.* **24**, 78; *Chem Abstr.* **2**, 1829 (1908)

[9] R. Granger, M. Corbier and J. Vinas, *C.R. Acad. Sci., Paris* **234**, 1058 (1952).

these Laboratories indicate a m.p. of 145°. In addition, m.ps for the isomer have been given from 135–148°[2,5,6,9–11] Kralt *et al.*, in pharmacological studies with N-alkyl substituted O-acetylsalicylamides were apparently unaware of the possible rearrangement in their systems.[12] Several analgesic and enzymic studies[13,14] using acetylsalicylamides have also been made without full cognizance of the instability of II. Another source of possible confusion rests in the fact that salicylamide (I) itself melts at 140° and gives an unusually sensitive ferric chloride test even in solutions less than 10^{-4} M. Since this test was one of the prime bases for assignment of structure IV[5,6] and because of the other noted discrepancies, a re-examination of the system was in order.*

Rearrangement of O-acetylsalicylamide (II).[17] Compound II rearranges irreversibly to a single isomer under a variety of conditions: (a) standing at room temperature in methanol, ethanol, pyridine or dilute alkali; (b) slow heating of the solid above 115°; (c) heating above 100° in certain solvents such as acetone (sealed tube).[18] In all cases the resulting isomer was the same by analytical criteria in solution (UV, NMR, IR, TLC); however, depending on its mode of formation the solid displayed different thermal behaviour. Several spectral and thermal analyses were employed to establish firmly the nature of the rearrangement and the structures of the isomers. These will be dealt with in turn; the results show that the original assignment of structure IV is correct. In addition, some unusual properties have been uncovered for both II and IV.

* When salicylamide (I; 0·06 mole) is added to Ac_2O (20 ml) containing pyridine (5 ml) at room temp, a pale pink soln forms which deposits a copious amount of white solid within 30 sec. After filtering and washing with benzene, the solid was recrystallized from benzene–AcOEt and again from AcOEt to give small plates (93%), capillary m.p. 144·2–145·3° (corr). The sample was homogeneous on thin layer plates using chf, acetone–chf, acetone–benzene and other developing media. The compound gave a negative $FeCl_3$ test in water, benzene or acetone, even after warming.[16] (Found: C, 60·2; H, 5·1; O, 26·5; calc. for $C_9H_9NO_3$: C, 60·33; H, 5·06; O, 26·79; N, 7·82%.) The ester has surprisingly low solubility in the usual solvents (diethyl ether, chf, benzene, pyridine, acetone, etc.). It dissolves readily in MeOH or EtOH but rapidly isomerizes. As discussed below, spectral data confirm structure II.[16]

[10] Kalle and Co., DRP 177054; *Chem. Zent.* II, 1789 (1906).

[11] W. L. Hicks, *J. Chem. Soc.* **97**, 1032 (1910).

[12] T. Kralt, H. D. Moed, E. J. Ariens and Th. Hendriksen, *Rec. Trav. Chim.* **78**, 199 (1959); **78**, 207 (1959). E. J. Ariens, T. Kralt and H. Moed, DRP 1,023,029, Jan. 23, 1958; *Chem. Abstr.* **54**, 22500h (1960).

[13] E. Hart, *J. Pharmacol.* **89**, 205 (1947).

[14] P. Bastide and G. Dastugue, *Thérapie* **9**, 360 (1954).

[15] S. Soloway and P. Rosen, *Analyt. Chem.* **24**, 979 (1952); **25**, 595 (1953).

[16] Compound I also forms adducts with HCl and acetyl chloride, both of unknown structure;[5,6] treatment of the adducts with water yields only the original salicylamide (I) and the isomer of II, respectively. For additional reports on haloacetyl adducts of I, and on the Fries rearrangement and isomerization in nitrobenzene of II, see R. Granger, M. Corbier and J. Vinas, *C. R. Acad. Sci., Paris* **233**, 578 (1951) and ref. 9.

[17] The related acyl migration in amino alcohols is well documented (G. L. Jenkins and W. H. Hartung, *Chemistry of Organic Medicinal Products* (3rd Edition) p. 351. Wiley, New York (1949) and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 5773 (1951). N-Acyl amides are of considerable interest in biochemical processes; see M. Shemyakin, V. Antonov, A. Shkrob, V. Shchelokov and Z. Agodzhanyan, *Tetrahedron* **21**, 3537 (1965).

[18] Compound II is reasonably stable in refluxing benzene, ethyl acetate or acetonitrile solutions and is fairly stable in acidified (HCl) acetonitrile but does isomerize slowly on long standing (>20 hr) in acid medium. The only exception found for the irreversible nature of the isomerization is the reformation of II in acetic acid solutions of the isomer.[5]

A. *Thermal isomerization.* Differential thermal analysis and examination under a microscope with a Kofler hot stage have revealed the following. When heated at the rate of 10°/min, II melts sharply at 142–144° (depending on fusion method); DTA shows a sharp exotherm immediately after the melting endotherm, indicating rearrangement to the more stable isomer (see Experimental section for large scale thermal reactions and details of product recovery and analysis). However, very slow heating (<5°/min) results in a softening at 115–120° and complete fusion at 120–123° with concomitant rearrangement. Compound II appears to exist in only one crystalline modification (rectangular plates), independent of the crystallizing medium (benzene, ethyl acetate, chloroform, acetonitrile and mixtures thereof). On the other hand, the isomer is obtained in at least three crystalline modifications, depending on the method of formation. One needle form undergoes partial melting and reorganization (Kofler

TABLE 1. IR ABSORPTIONS[a] OF II AND RELATED COMPOUNDS

	I		II		Phenyl acetate	
Assignment	KBr	$CHCl_3$[d]	KBr	$CHCl_3$[d]	Neat	$CHCl_3$
Amide N—H	3400 (s)	3500 (s)	3380 (s)	3500 (s)		—
Amide N—H	3190 (s)	3380 (s)	3170 (s)	3380 (s)		—
Ester carbonyl		—	1745 (m)	1770 (s)	1775 (s)	1755 (s)
Amide-I	1680 (s)	1658 (s)	1675 (s)	1680 (s)		—
Amide-II	1630 (s)	1618 (m)	1631 (s)	1588 (m)		—
Acetate		[c]	1196 to 1224 (s)[b]	1185 to 1200 (s)	1190 to 1225 (s)	1190 to 1250 (s)

[a] Reported in cm^{-1}. [b] Broad doublet. [c] Almost no absorption from 1100–1250 cm^{-1}. [d] Relatively weak spectra due to solubility problem.

hot stage; imperceptible in capillary melting) to another needle form at 120–124°, followed by sharp melting at 140–142°. A third form, rectangular plates, fuses from 137–140°, but cooling gives the customary higher melting needles. The plates gave a capillary m.p. of 146·0–146·8°.

Thus, the diverse m.ps reported in the literature for II and its isomer could be due to a variety of causes; for example, different rates of heating,[6] purity of sample, method of purification and uncorrected data.

An attempt was made to distinguish between the isomers by mass spectroscopy (CEC 110B spectrometer). However, both spectra were identical but for small differences in relative intensity: *m/e* 179 (380), 137 (1310), 120 (2100), 92 (750), etc. While II and IV could conceivably give rise to identical mass spectra, it is believed that II isomerizes at the inlet (100°).

B. *Infrared spectra.* Tables 1 and 2 give pertinent IR spectral data for I, II, the isomer, and related compounds. Compound II shows absorption typical of a primary amide (cf. salicylamide) as well as that of an acetate (cf. phenyl acetate). The N—H and carbonyl absorptions of the isomer are in consonance with the imide structure (IV) (cf. N-acetylbenzamide and V, as well as ergotinine[19,20]). The secondary amide character of structure III generally shows split N—H absorptions and at considerably higher frequency (40–60 cm^{-1}); carbonyl bands for such a structure invariably appear well below 1700 cm^{-1} unlike the present case.[19] The lower energy carbonyl bands in

[19] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Edition) pp. 209–229. Wiley, London (1962).

[20] L. Marion, D. Ramsay and N. R. Jones, *J. Amer. Chem. Soc.* 73, 305 (1951).

IV relative to N-acetylbenzamide are undoubtedly due to hydrogen bonding (see O—H absorptions, Table 2).

C. *NMR spectra.* The rearrangement was readily followed by PMR; the data are summarized in Tables 3 and 4. A saturated solution of II in pyridine (0·91 F; some

TABLE 2. IR ABSORPTIONS[a] OF IV AND RELATED COMPOUNDS

Assignment	IV		N-Acetylbenzamide[c]		V[d]
	KBr	$CHCl_3$[d]	KBr	$CHCl_3$[d]	$CHCl_3$
N—H	3400 (w)	3400 (w)	3370 (w)	3400 (w)	3410 (w)
O—H	3279–3086 (m)[b]	3275–3010 (w)[b]	—		—
Imide-Carbonyl	1721 (s)	1720 (s)	1740 (s)	1715 (sh)	1710 (s)
	1652 (s)	1680 (s)	1720 (sh) 1682 (m)	1695 (s)	1680 (sh)
Ester carbonyl	—		—		1775 (m)

[a] Reported in cm $^{-1}$. [b] Broad doublet. [c] Prepared according to C. Hurd and A. Prapas, *J. Org. Chem.* **24**, 388 (1959); m.p. 117–118° (lit. 117°). [d] Relatively weak spectra due to solubility problem. [e] O,N-Diacetylsalicylamide, prepared by Ac_2O acetylation of II or IV; m.p. 64·0–65·5° (sublim.) (lit. 65°)[6]. Treatment of IV with acetic *acid* provides the only method for reversible formation of II.

TABLE 3. NMR SPECTRAL DATA[a]

Compound	O-Acetyl CH_3	N-Acetyl CH_3	N-H(O—H)	Phenyl
		IN PYRIDINE:		
II	2·23	—		
Phenyl acetate	2·20	—		
IV	—	2·63		[b]
N-Acetylbenzamide	—	2·63		
		IN ACETONE-D_6		
II	2·27(3·0)	—	6·4–8·3(6·0)	
Phenyl acetate	2·22(3·0)	—	—	7·0–7·5(5·1)
IV	—	2·46(3·0)	6·8–8·2(6·1)	
N-Acetylbenzamide	—	2·45(3·0)	9·4–10·3(1·5)	7·5–8·2(5·0)

[a] Recorded on a Varian A-60 instrument for freshly prepared solutions (0·7–1·0F). Chemical shifts (δ) are relative to internal TMS and integrated areas are shown in parentheses.
[b] Phenyl and N-H(O—H) obscured by pyridine absorption.

TABLE 4. ISOMERIZATION OF II IN ACETONE-D_6 AT 130°

Time, Min	Relative area at δ: 2·27	2·46	6·4–8·2	Total CH_3 area relative to phenyl = 4
0	1·0	0	2·0	3·0
15	1·0	1·0	2·9	2·8
55	1·0	6·7	16	1·9
515	0	0	—	0

undissolved solid) was allowed to stand at 30° under nitrogen in a sealed NMR tube. Except for aromatic and N—H absorption (obscured by that of pyridine), the initial spectrum (Varian A-60) displayed only a sharp singlet at δ 2·23 (relative to internal TMS), whose intensity steadily decreased as a new singlet appeared at δ 2·63. After

five days, integration showed 16% II and 84% IV. In addition, the entire sample had dissolved; compound IV is expected to have greater solubility than II in pyridine. Under the same conditions, phenyl acetate (1·4 F) displayed a singlet at δ 2·20, while N-acetylbenzamide (0·91 F) showed a singlet at δ 2·63; both spectra remained unchanged after at least 15 days.

In another experiment, a saturated solution of II in fresh acetone-d_6 (Merck, Sharp and Dohme) (0·90 F) (some undissolved solid) was sealed under nitrogen in an NMR tube. The spectrum was indefinitely stable at room temperature; however,

TABLE 5. UV SPECTRAL DATA[a]

Compound	CH_3CN	CH_3CN + Base[c,d]	CH_3OH	CH_3OH + Base[c,d]
II	268 (max) 825 255 (min) 790 222 (sh) 7950	Instantaneous isomerization to anion of IV	(see text)	
I[b]	304 (max) 4910 262 (min) 590 235 (max) 7900 224 (min) 6800 204 (max) 41800	340 (max) 7460 282 (min) 545 250 (max) 7820 237 (min) 6100 216 (max) 30000	302 (max) 3800 262 (min) 274 235 (max) 7120 224 (min) 6020 204 (max) 39100	330 (max) 6020 262 (min) 550 243 (max) 6700 234 (min) 6020 215 (sh) 31500
IV	308 (max) 4200 270 (min) 1060 244 (max) 12300 232 (min) 9600 208 (max) 26400	367 (max) 7600 295 (min) 895 257 (sh) 7170 228 (max) 38400 206 (min) 13900	306 (max) 4230 270 (min) 1120 243 (max) 12300 233 (min) 11100 209 (max) 28100	352 (max) 6350 288 (min) 249 254 (max) 8350 247 (min) 8100 225 (max) 37500 207 (min) 9380

[a] Recorded on a Beckman DK-2A spectrophotometer; wavelength in mμ, absorptivity in l./mole-cm.

[b] Spectra essentially the same as in aqueous soln.[8a]

[c] Addition of 0·1–0·2 ml. of 0·1N NaOH (aq) to 3–3·5 ml. soln. (sample and reference).

[d] The apparent pK_a's of I and IV were measured potentiometrically; in acetonitrile, the values are 9·0 and 8·1, respectively; in MeOH, 8·8 and 7·8. Only one equivalent of base (0·1N NaOH) is consumed, giving only one inflection point. Addition of acid (HCl) to neutral solns caused no change in the spectra.

the rearrangement took place at a convenient rate at 130°. The spectrum was recorded at set intervals after quenching the reaction in ice water. The entire sample dissolved at 130°, but always remained partially undissolved at room temperature. In a separate experiment, it was found that the solubilities of II and IV in acetone (d_0) at room temperature are approximately the same. Under identical conditions, phenyl acetate gave a singlet (δ 2·22); there was no change in the spectrum after heating at 130° for more than 10 hr. N-Acetylbenzamide also gave a singlet (δ 2·45) but after heating at 130° the intensity decreased until after 6 hr 20% of the methyl hydrogens had exchanged. The integrated area of the phenyl region was unchanged. The exchange was obvious from another source. All spectra using acetone-d_6 as solvent exhibited a well defined quintuplet centered at δ 2·17, assigned to acetone-d_5 impurity. The intensity of this multiplet in spectra recorded before heating was less than 1% of the total area. The increase in intensity was gauged by following the acetone-d_5 to phenyl area ratio. The N—H initially appeared as a broad singlet, δ 9·4–10·3, which disappeared completely after heating (130°) for less than 3 hr.

Examination of Table 5 reveals the following: (a) II isomerizes to IV with a half

life of 15 min. A plot of log (O-acetyl methyl integrated area) *vs* time gave an excellent straight line (12 points) over 4 half lives; least squares analysis gave the first order expression $k^{130°} = 7{\cdot}0 \pm 0{\cdot}3 \times 10^{-4}\ sec^{-1}$ (acetone-d_6). (b) The total methyl absorptions gradually decrease in intensity with complete disappearance after 515 min. At this time, acetone-d_6 is the most intense absorption. Since phenyl acetate does not exchange under these conditions, it is assumed that only the N-acetyl methyl (compound IV) does. This assumption is further supported by the excellent fit to first order kinetics, which were measured by the loss in area of O-acetyl methyl.

The exchange on CH_3 would appear to rule out structure III for the isomer. An equilibrium mixture of III and IV is possible; however, only two (eventually only one) methyl absorptions are evident. In addition, methyl protons in ketals and hemiketals of structure $CH_3C(OR)_2(X)$ are considerably less deshielded than in acyl functions and absorb 1·5–2·0 ppm further upfield.[21] The possibility that compound III does exist (other than as a short lived intermediate, e.g.) at 130° but not at the temperature (30–35°) during recording of spectra is considered highly unlikely (cf. the chroman-2-ols[22]).

Finally, it can be shown that the *ortho* hydroxyl of IV has an accelerating effect on methyl exchange. After 115 min at 130°, 70% of all methyl hydrogens had exchanged; as mentioned above, only 20% exchange occurred in N-acetylbenzamide after 350 min.

D. *Ultraviolet spectra.* Table 5 summarizes the UV spectra of I, II and IV in acetonitrile; the spectra in methanol (Table 5) are nearly identical for the neutral solutions (except for II, which isomerizes to IV with $t_{1/2}^{35°} \sim 6hr$). The data for II may be compared with that for phenyl acetate (in EtOH): λ_{max} 266(ε 400)[23] and benzamide (in EtOH): λ_{max} 268(ε 631), 259(min) (562), 242(sh) (7590).[24] The N-acetyl group in IV does not qualitatively alter the spectrum of I, but merely imposes a fairly uniform bathocromic shift (4–9 mμ) in both methanol and acetonitrile.

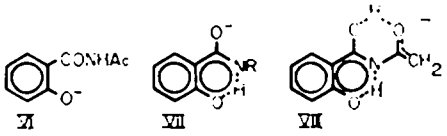
However, addition of base reduces somewhat the spectral similarity between I and IV. Salicylamide (I) in alkaline solutions has essentially the same spectrum in water, methanol or acetonitrile. On the other hand, IV exhibits a slight solvent effect, particularly in the long wavelength transition:

Salicylamide (I)			IV	
Water[25]	Methanol	Acetonitrile	Methanol	Acetonitrile
299 → 329	302 → 330	304 → 340	306 → 352	308 → 367
236 → 242	235 → 243	235 → 250	243 → 254	244 → 257

In methanol and acetonitrile, both I and IV are monobasic acids toward NaOH (aq); IV is the stronger acid in both solvents (see footnote d, Table 5). Much discussion has appeared concerning the silver, sodium and ammonium salts of IV;[6] based on analogy and chemical reactivity the salts have been assigned a simple phenoxide structure (VI).[6] The shift in alkaline solutions of acetonitrile (59 mμ) and methanol (46 mμ) for the "phenol" band in IV compared to the 'normal' shift (~30 mμ)[25]

[21] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* pp. 53–55, 57. Pergamon Press, New York (1959).
[22] L. I. Smith and R. B. Carlin, *J. Amer. Chem. Soc.* **64**, 435 (1942).
[23] G. Cilento and W. F. Walter, *J. Amer. Chem. Soc.* **76**, 4469 (1954).
[24] P. Grammaticakis, *Bull. Soc. Chim. Fr.* 207 (1953).
[25] L. Doub and J. M. Vandenbelt, *J. Amer. Chem. Soc.* **71**, 2414 (1949); E. W. Crandall and J. Olguin, *J. Org. Chem.* **31**, 973 (1966).

observed for I suggests the contribution of another structure for the anion. The non-classical aromatic structure VII (R = acetyl) is one possibility. Structure VIII is also an attractive candidate, particularly in acetonitrile; such structures are expected to be relatively unstable in the protic, more highly solvating MeOH–MeO^- medium.[25] Even salicylamide anion itself shows a slight solvent effect in acetonitrile in the same direction as IV; it is not known whether structure VII (R = H) is actually responsible, but this matter will be investigated. The structural feature of a hydrogen bridged aromatic ring (VII) has been suggested for another system.[26]



VI VII VIII

Acidification of the alkaline solutions in both solvents regenerated the original spectra. There was no evidence for chemical reaction or charge transfer interaction in either case. While there is no evidence from this or any other of the spectral analyses for its existence as an isolable species, III is a very likely intermediate for the presumably intramolecular acetyl migration.

EXPERIMENTAL[27]

Isomerization of O-*acetylsalicylamide* (II). As discussed above, isomerization occurs in many ways. In one experiment, a MeOH solution of II (10% w/v) was refluxed for several hr. After evaporation of the solvent, the white solid residue was recrystallized from benzene–AcOEt and again from AcOEt to give long, thick needles, capillary m.p. 141·5–143·0°, in nearly quantitative yield. The sample analyzed correctly for $C_9C_9NO_3$ and gave a strong $FeCl_3$ test. However, it did not form an indophenol; other specially substituted phenols are known to fail this very sensitive color reaction.[28] The compound was homogeneous by TLC and had distinctly different R_f values from I or II.

Thermal measurements. The thermal history of solid II was followed on a Du Pont 900 Differential Thermal Analyzer. At a heating rate of 10°/min in N_2 atm, a fairly sharp endotherm was observed at 142–144°, immediately followed by a sharp exotherm (144–146°). After cooling, another thermograph of the same sample gave only a broad endotherm from 129–138°. On a larger scale, a sample of II was sealed under N_2 in a glass tube and heated for 2 hr at 160°. The recovered solid was recrystallized from benzene–AcOEt giving white solid, m.p. 143–144° (needles); a positive $FeCl_3$ test was observed. However, this apparently straight forward result was complicated by the following: if the recovered solid was vacuum sublimed, the sublimate gave a strong $FeCl_3$ test and an IR spectrum (KBr, $CHCl_3$) identical with that of the recrystallized sample. Yet the solid melted at 120–124°, partially resolidified and remelted at 138–140°. This same behaviour was observed in the product of only one other isomerization method, *viz.*, the warming of a pyridine–EtOH soln of II on a steam bath, followed by partial evaporation to yield crystals (needles). Finally, both II and its isomer were carefully examined under a microscope on a Kofler hot stage illuminated with polarized light. When heated fairly rapidly (10°/min) II melted sharply at 142°. However, very slow heating (< 5°/min) resulted in a softening at 115–120° and complete fusion at 120–123°. That this observation is not due to polymorphism of II was shown by a positive $FeCl_3$ test, TLC, and an IR spectrum (identical to that of the pure isomer) of the recovered melt.

[25] L. C. Dorman, *Tetrahedron Letters* No. 4, 459 (1966). For another viewpoint, see O. L. Chapman, *Tetrahedron Letters*, No. 23, 2599 (1966).

[27] All capillary m.ps are corrected; the micro m.ps for "normal" compounds on the hot stage used agree with those of capillary measurements; e.g., salicylamide (Eastman White Label), capillary m.p. 139·5–140.2° and micro m.p. 140·5–141·0°. The possibility that II or IV released ketene (or$(C_2H_2O)_n$) during heating to leave salicylamide was ruled out by IR spectra and tlc of the recovered melt.

[28] M. Bohdanecky, *Chem. Průmysl*, 4, 25 (1954); *Anal. Abst.* 2, 2473 (1955). F. Feigl, *Spot Tests in Organic Analysis*, 6th ed., p. 202. Elsevier Pub. Co., New York (1960).

Similar examination of the pure isomer (as obtained from MeOH treatment of II) showed the following, independent of heating rate: the needles underwent partial melting and reorganization (imperceptible in capillary melting) from 120–124° followed by sharp melting at 141–142°. Several fusion-solidification cycles produced no change in the final m.p. (the crystalline transformation at 120° was no longer observed after the initial cycle). A third modification of IV was also detected; acidification of a dil NaOHaq solution of IV (or II) gave white powder, whose particles were tiny, rectangular plates—large needles were obtained by all other isomerization or purification methods. The capillary m.p. 146·0–146·8° agrees with that of an early report[8]; however, slow heating on the Kofler hot stage effected gradual fusion from 137–140°. When cooled, the customary large needles developed. The possibility that a third isomer (perhaps III) was actually being observed is considered unlikely since (somewhat surprisingly) the solid state IR spectra (KBr) for IV obtained by all methods were identical except for small differences in relative intensities. The existence of a solvate for II or IV was precluded by analysis and the fact that the fusion behaviour (Kofler) was identical for samples prepared in several crystallizing media.