Tetrahedron. Vol 29, pp. 3173 to 3176. Pergamon Press 1973. Printed in Great Britain

BENZISOXAZOLIUM CATIONS—II[a]

REACTION WITH ANTHRANILIC ACID: INTRAMOLECULAR REACTION OF AN N-AROYL-N-ALKYLSALICYLAMIDE

G. SUBRAHMANYAM* and T. DUTTA ROY
Department of Chemistry, Indian Institute of Technology, Kharagpur, India

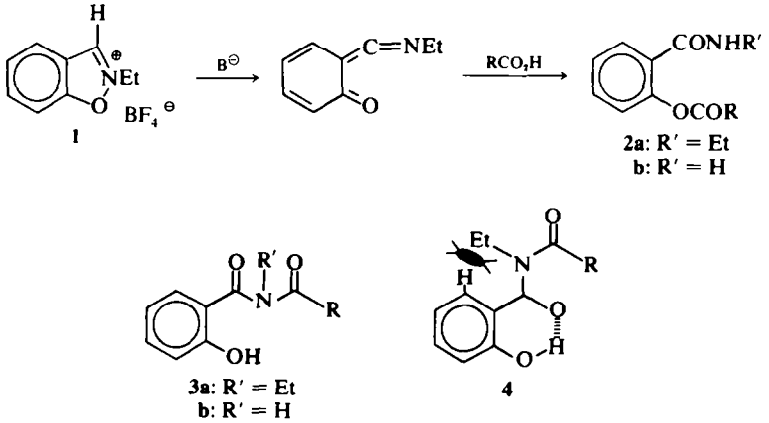
(*Received in the UK* 8 *March* 1973; *Accepted for publication* 12 *June* 1973)

Abstract—Reaction of 2-ethylbenzisoxazolium fluoborate (**1**) with anthranilic acid gives O-aroylsalicylamide (**5a**) and the quinazolone (**6a**), whose structure is established by an unambiguous synthesis of its methyl ether (**6b**). The O-aroyl amide (**5a**), formed *via* the ketoketenimine (Scheme 1) from the salt **1**, undergoes O→N migration to the imide (**8**) which through an intramolecular reaction followed by dehydration is converted to the quinazolone **6a** (Scheme 2). Independently the O-aroyl amide (**5a**) could be transformed to the quinazolone (**6a**) under basic conditions. The formation of quinazolone (**6a**) suggests the labile N-alkyl-N-aroyl isomer (**8**), which is expected to be in equilibrium with the O-aroyl isomer (**5a**), is captured. (Scheme 2).

N-Alkylbenzisoxazolium salt (**1**) reacts with carboxylic acids in the presence of base to give O-acyl-N-alkylsalicylamides (**2a**) which are readily saponified at pH 8–10 (Scheme 1).[2] No N-acylisomer (**3a**) was detected. On the other hand, O-acylsalicylamides (**2b**) are readily transformed to N-acylsalicylamides (**3b**) under alkaline conditions.[3,4] The formation of O-acylisomer (**2a**), only when an alkyl group is present on the amide nitrogen, has been explained by Kemp and Woodward[2] as due to a steric interaction in the N-acylisomer (**3a**) shown in **4**. The N-Et group was thought to prevent the imide CO group from achieving coplanarity with the benzene ring. Recent kinetic investigations by Russel *et al.*[5] suggested that the earlier difficulty in isolating the N-acyl products may not be due to a steric effect, but to increased susceptibility of the N-acyl isomers (**3a**) to solvolysis. In the light of above observations, we considered the possibility of capturing the labile N-acyl isomer (**3a**) and report the results in this direction.

The N-acyl amide (**3a**) must be present in small concentration in equilibrium with the O-acyl isomer (**2a**) under basic conditions. Since it has been observed that the N-acyl isomers (**3a**) are rapidly solvolysed,[5] an intramolecular reaction of a strategically situated nucleophile might trap the N-acyl amide (**3a**). Shemyakin *et al.*[6] remarked that the reactivities of the CO group of N-acyl amides are comparable with those of aldehydes and ketones and utilised them for the synthesis of cyclic peptides *via* the nucleophilic attack of an amino group at the imide CO group. Consequently, an amino group was thought to be an ideal nucleophile to trap

[a]Part I, Ref 1.



SCHEME 1

the N-acyl amide (**3a**).[7] In order to prepare the O-aroylisomer (**5a**) which has a nucleophile (amino group), we studied the reaction of the isoxazolium salt (**1**) with anthranilic acid under alkaline conditions and isolated two products, m.p. 146–147° and m.p. 207–208°. In the mass spectrum of the product, m.p. 146–147°, the molecular ion at *m/e* 284 (19%) was accompanied by peaks at *m/e* 239 (2·5%), 148 (14%), 120 (100%), 92 (50%) and 65 (29%). The NMR* spectrum contained a triplet at δ 0·98 (J = 7 Hz, —N—CH_2CH_3), a multiplet at δ 3·34 (—N—CH_2CH_3), broad peaks at δ 5·85 and 6·47 (—NH_2 and —CONH—) and a multiplet at δ 6·6–8·09 (aromatic 8H) consistent with the structure **5a**. The second product, m.p. 207–208°, displayed the NMR* signals at δ 1·15 (t, J = 7 Hz, —N—CH_2CH_3), δ 4·08 (q, J = 7 Hz, —N—CH_2CH_3), δ 6·76–8·1 (aromatic 8H) and δ 9·8–10·28 (phenolic OH). In conjunction with UV and IR evidence, these data permitted a quinazolone structure, **6a**, for the higher melting compound. This structural assignment received additional support from the mass spectrum which showed the molecular ion at *m/e* 266 (39%) and other prominent peaks at *m/e* 265 (100%), 249 (24%), 238 (9%), 119 (27%), 92 (13%) and 65 (6%). The characteristic fragmentation pattern is shown in Fig 1.[8,9] The quinazolone (**6a**) could be readily converted to its methyl ether (**6b**) whose structure was unequivocally confirmed by an independent synthesis. Condensation of anthranilamide with *o*-anisoyl chloride furnished the amide (**7**) which

*100 MHz spectrum.

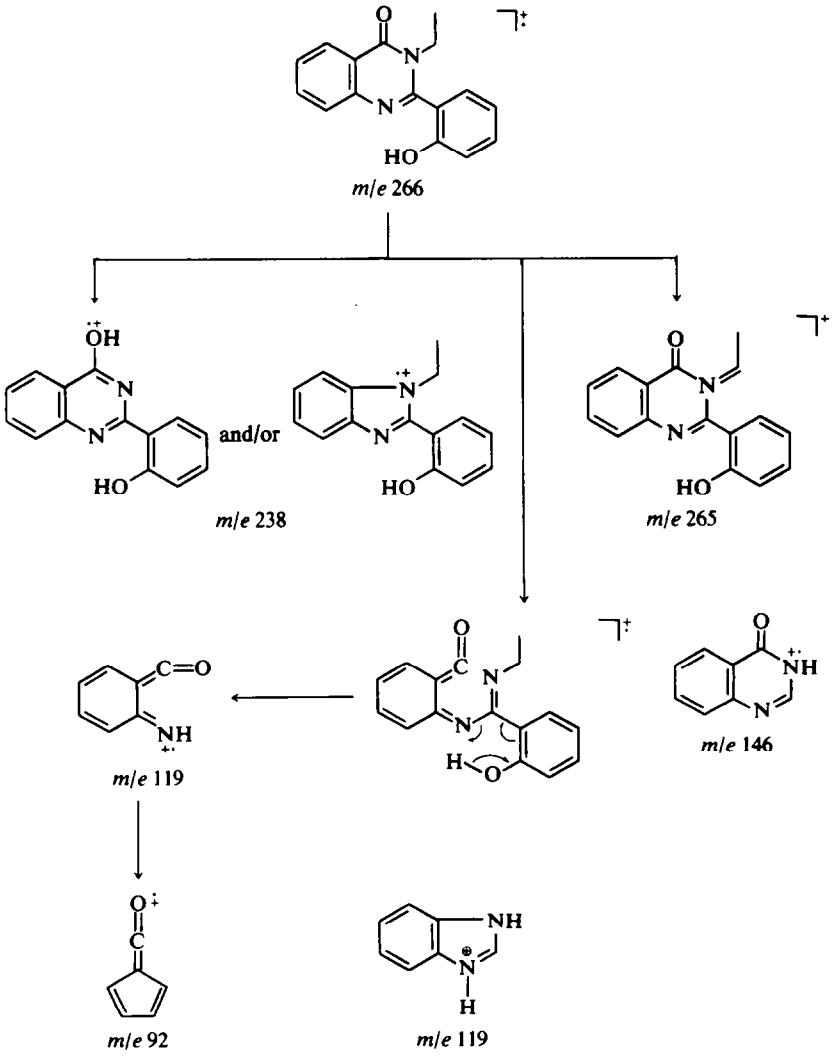
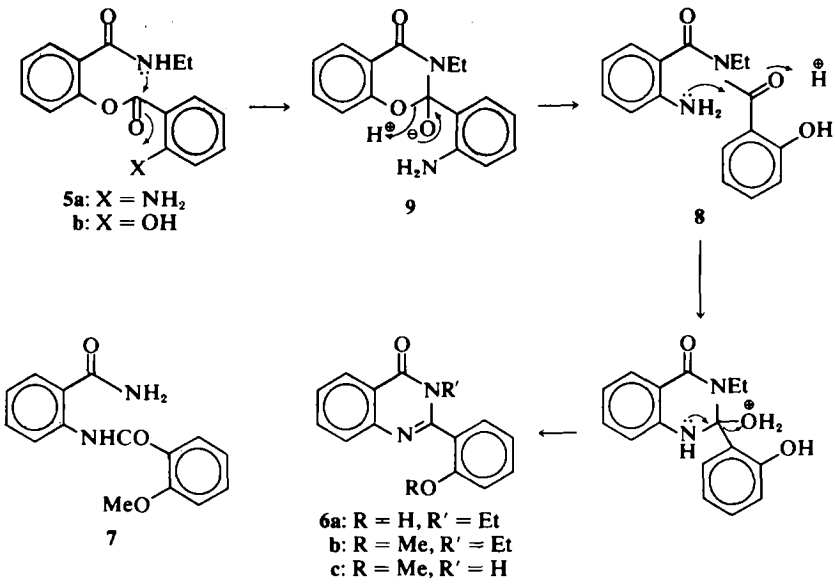


Fig 1. Proposed mass spectral fragmentation of **6a**.



SCHEME 2

underwent cyclization with 10% alkali to the quinazolone (**6c**).[10-12] N-Ethylation of the quinazolone (**6c**) with ethyl iodide in the presence of sodium ethoxide gave the N-ethylquinazolone (**6b**). The amide (**5a**) was converted to the quinazolone (**6a**) under the influence of triethylamine in DMF or sodium bicarbonate in ethanol. Analogous reaction of salicylic acid with the salt (**1**) yielded the phenolic amide (**5b**) which remained unchanged in the presence of triethylamine in DMF.

The formation of the phenolic amide (**5a**) is unexceptional as it is formed by the reaction of anthranilic acid on the ketoketenimine, produced by the cleavage of the isoxazolium salt (**1**) with base, followed by rearrangement (*cf* Scheme 1). A mechanism for the formation of quinazolone (**6a**) can be rationalized as occurring through intermediacy of the N-aroyl isomer **8** (Scheme 2). Attack of the amide on the ester carbonyl, *via* the tetrahedral intermediate (**9**) would lead to the N-aroyl isomer (**8**), which can undergo intramolecular reaction followed by dehydration to furnish the quinazolone (**6a**).

EXPERIMENTAL

M.ps are uncorrected. Solvent extracts were dried over Na_2SO_4.

IR spectra were taken on a Perkin–Elmer Infracord model 137B as Nujol mulls or KBr pellets. UV spectra were recorded on a Unicam model 700 spectrophotometer in 95% EtOH. PMR spectra were scanned on Varian A-60 and HA-100 instruments with TMS as internal standard ($\delta = 0$) in $CDCl_3$ unless otherwise stated. Mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionising potential of 70 eV and an acceleration voltage of 3 kV.

TLC were carried out on silica gel (200 mesh) containing 15% gypsum as binder. Visualisation of zones after development was by I_2-vapours.

Reaction of anthranilic acid with benziosoxazolium fluoborate (**1**)

To a cold stirred soln of anthranilic acid (274 mg, 2 mmoles) in NaOHaq (1N, 2·5 ml) overlayered with EtOAc (10 ml) was added finely divided **1** (470 mg, 2 mmoles) over a period of 5 min. The initial pH of 8–9 of the mixture changed to pH 5–6 at the end of the reaction. Water (10 ml) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3× 10 ml). The combined EtOAc extracts were washed with water (10 ml) and dried. the residue (607 mg), obtained after removal of the solvent, was processed as follows.

(a) Crystallisation of the residue from EtOAc-light petroleum afforded O-(2-*aminobenzoyl*)-N-*ethylsalicylamide* (**5a**) (236 mg), m.p. 146–147°; λ_{max}^{EtOH} 254 (ε 1065), 288 (ε 2911), 302 (ε 2840), 317 nm (ε 2769); ν_{max}^{Nujol} 3250 (NH), 1690 (ester C=O), 1640 (amide C=O) cm^{-1}. (Found: C, 67·63, H; 5·87, N, 9·73. Calc. for $C_{16}H_{16}N_2O_3$: C, 67·61; H, 5·63, N, 9·83%).

Concentration of the mother liquors from the above crystallisation yielded 3-*ethyl*-2(o-*hydroxyphenyl*)-4-*quinazolone* (**6a**; 34 mg),* m.p. 207–208°; λ_{max}^{EtOH} 233 (ε 26600), 279 (ε 9493), 304 nm (ε 3555); ν_{max}^{Nujol} 3100 (broad, OH), 1690 (amide C=O) cm $^{-1}$. (Found: C, 71·68; H, 5·58; N, 10·63. Calc. for $C_{16}H_{14}N_2O_2$: C, 72·18; H, 5·26; N, 10·52%).

(b) The residue was refluxed with $NaHCO_3$aq in EtOH (20 ml, $NaHCO_3$ was dissolved in minimum volume of water and made 1% with EtOH) for ½ hr. EtOH was removed *in vacuo*, water (10 ml) added, and extracted with $CHCl_3$ (3× 10 ml). The extract was washed with water and

*The yield varied slightly in each experiment.

the solvent removed to get a residue (480 mg), which on crystallisation from EtOAc-light petroleum, furnished **6a** (302 mg), m.p. 207–208°.

Reaction of O-(2-*aminobenzoyl*)-N-*ethylsalicylamide* (**5a**) *with bases*

(a) *With* DMF-NEt_3. **5a** (142 mg, 0·5 mmole) in DMF (5 ml) containing NEt_3 (50 mg, 0·5 mmole) was left at room temp for 20 hr and warmed at 50–60° for 1 hr. Water (20 ml) and EtOAc (20 ml) were added, the layers separated, and the aqueous layer extracted with EtOAc (3× 10 ml). Removal of the solvent and crystallisation of the residue from EtOAc-light petroleum gave **6a** (60 mg), m.p. 207–208°.

(b) *With* $NaHCO_3$ aq alc. **5a** (100 mg) was refluxed with $NaHCO_3$aq alc (1%, 10 ml) for ½ hr. Usual work up and crystallisation of the crude product furnished **6a** (60 mg), m.p. 207–208°.

O-(2-*Hydroxybenzoyl*)-N-*ethylsalicylamide* (**5b**)

Reaction of salicylic acid (138 mg, 1 mmole) in NaOHaq with 1 (235 mg, 1 mmole) as described in the case of anthranilic acid gave a crude residue (344 mg) which was crystallised from benzene-light petroleum to yield a white feathery solid (**5b**) (169 mg); m.p. 134–135°; λ_{max}^{EtOH} 238 (ε 16720), 304 nm (ε 7219); ν_{max}^{Nujol} 3300 (OH), 1640 (amide C=O), 1700 (ester C=O) cm^{-1}; PMR (100 MHz): δ_{CDCl_3} 0·99 (3H, t, J = 7 Hz), (—N—CH_2—CH_3); 3·31 (2H, m), (—N—CH_2—CH_3); 6·22 (1H, broad s, partly exchangeable with D_2O), (—NH); 6·88–8·07 (8H, m), (aromatic H); 10·33 (1H, s, partly exchangeable with D_2O), (OH). (Found: C, 67·43; H, 5·13; N, 4·92. Calc. for $C_{16}H_{15}NO_4$: C, 67·38; H, 5·27; N, 4·91%).

Treatment of **5b** *with* DMF-NEt_3. A soln of **5b** (69 mg) and NEt_3 (50 mg) in DMF (5 ml) was left for 20 hr at 25° and then warmed for one hr at 50–60°. After work up, the starting material was recovered.

3-*Ethyl*-2(o-*methoxyphenyl*)-4-*quinazolone* (**6b**). A mixture of **6a** (200 mg) in acetone (15 ml), anhy K_2CO_3 (2 g) and MeI (1 ml) was gently refluxed on a water bath for 8 hr adding MeI (0·5 ml) twice during an interval of 3 hr. The mixture was then filtered from the solid portion and repeatedly washed with acetone. The solvent was removed and the resulting solid residue was dissolved in water (20 ml) and extracted with $CHCl_3$ (3×20 ml). The foregoing solid portion was dissolved in water and extracted with $CHCl_3$ (2× 15 ml). The combined chloroform extracts were successively washed with 2% NaOHaq and water and dried. Removal of the solvent gave a gummy residue (220 mg), which on crystallisation from EtOAc-light petroleum, furnished **6b** (140 mg), m.p. 161–162°; ν_{max}^{Nujol} 1670 (amide C=O) cm^{-1}; PMR (100 MHz): δ_{CDCl_3} 1·17 (3H, t), (—N—CH_2—CH_3); 3·5–4·46 (2H, m), (—N—CH_2—CH_3); 3·82 (3H, s) (—O—CH_3); 7·0–8·4 (8H, m), (aromatic H); MS (*m/e*): 280 (M^+, 100%), 279 (100%), 261 (39%), 250 (67%), 248 (100%), 146 (13%), 119 (45%). (Found: C, 73·21; H, 5·53; N, 10·02. Calc. for $C_{17}H_{16}N_2O_2$: C, 72·85; H, 5·70; N, 10·0%).

N-(o-*Methoxybenzoyl*) *anthranilamide* (**7**). To an ice-cold soln of anthranilamide[13] (1 g, 7·3 mmoles) in pyridine (3 ml) was added o-anisoylchloride (1·25 g, 7·3 mmoles) and the mixture shaken vigorously when a fluffy mass separated. The mixture was heated on a water bath for 1 hr, water (30 ml) added, and acidified with dil HCl to pH 3. The resulting solid was then filtered, washed with water and dried. Crystallisation from EtOH gave a white solid (1·2 g), m.p. 219–220°; ν_{max}^{KBr} 1650 (amide C=O) cm^{-1}; MS (*m/e*): 270 (M^+, 6·2%). (Found: C, 66·63; H, 5·15; N, 10·12. Calc. for $C_{15}H_{14}N_2O_3$: C, 66·67; H, 5·18; N, 10·37%).

2-(o-*Methoxyphenyl*)-4-*quinazolone* (**6c**). **7** (300 mg) was refluxed with 10% NaOHaq in EtOH (30 ml, NaOH was dissolved in minimum volume of water and the resulting soln was made 10% with EtOH) for 1 hr. EtOH was then removed *in vacuo* to furnish an oily residue. Water (20 ml) was then added, acidified with HOAc, and extracted with $CHCl_3$ (3×15 ml). The extract was washed with water and dried. Removal of the solvent gave a solid residue which on crystallisation from EtOAc-light petroleum furnished white needles of **6c**, m.p. 204–205°; PMR (60 MHz): δ_{CF_3COOH} 4·25 (3H, s), (O—CH_3): 7·21–8·51 (m, aromatic H). (Found: C, 71·23; H, 4·56; N, 10·92. Calc. for $C_{15}H_{12}N_2O_2$: C, 71·44; H, 4·76; N, 11·11%).

3-*Ethyl*-2-(o-*methoxyphenyl*)-4-*quinazolone* (**6b**). A soln of **6c** (200 mg) in abs EtOH (20 ml) was added to a refluxing soln of Na (120 mg) in EtOH (50 ml). EtI (0·5 ml) in alcohol (2 ml) was added followed by Na (120 mg). The alternate addition of alc EtI and Na in the same amounts was repeated 6 times at an interval of 20 min (total reaction period was 2 hr). EtOH was removed *in vacuo*, water (30 ml) was added and extracted with $CHCl_3$ (3×20 ml). The $CHCl_3$ extract was washed with water (4×15 ml) and the solvent was removed and the gummy residue (204 mg) was crystallised from ether-light petroleum to get **6b** (60 mg), m.p. 161–162°.

The m.p. of this compound remained undepressed on admixture with **6b**, obtained earlier on methylation of **6a**. Moreover the IR spectra of these two compounds are superimposable.

Acknowledgement—The authors wish to thank professors M. V. Bhatt, T. R. Govindachari and Dr. H. J. Ringold for the NMR and mass spectra and professor P. Brown for the mass spectra and suggestions.

REFERENCES

[1]G. Subrahmanyam and M. Jogibhukta, *Tetrahedron* **27**, 5229 (1971)
[2]D. S. Kemp and R. B. Woodward, *Ibid.* **21**, 3019 (1965)
[3]J. McConnan and A. W. Titherley, *J. Chem. Soc.* 1318 (1906)
[4]A. J. Gordon, *Tetrahedron* **23**, 863 (1967)
[5]P. L. Russel, R. Malcolm Topping and D. E. Tutt, *J. Chem. Soc.* (B), 657 (1971)
[6]M. M. Shemyakin, V. K. Antonov, A. M. Shakrob, V. I. Schehelokov and Z. E. Agadzhanylan, *Tetrahedron* **21**, 3537 (1965)
[7]*cf* [a]O. Mumm and C. Bergel, *Chem. Ber.* **45**, 3149 (1912); [b]R. B. Woodward and R. A. Olofson, *Tetrahedron Suppl.* **7**, 415 (1966), see p. 429
[8]S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson and H. Budzikiewicz, *Ibid.* **19**, 1011 (1963)
[9]C. Bogentoft and B. Danielsson, *J. Het. Chem.* **2**, 193 (1972)
[10]H. Stephen and G. Wadge, *J. Chem. Soc.* 4420 (1956)
[11]V. S. Patel and S. R. Patel, *J. Ind. Chem. Soc.* **42**, 531 (1965)
[12]S. C. Pakrashi, A. De and S. Chattopadhyay, *Ind. J. Chem.* **6**, 472 (1968)
[13a]R. P. Steiger and E. C. Wagner, *J. Org. Chem.* **13**, 347 (1948); [b]E. H. Rodd, *Chemistry of Carbon Compounds* Vol. 3 Part A, p. 578. Elsevier, New york (1954)