SYNTHESIS AND RING-CHAIN ISOMERISM OF N-MONOSUBSTITUTED 4-BENZOYLNICOTINAMIDES AND 3-BENZOYLISONICOTINAMIDES

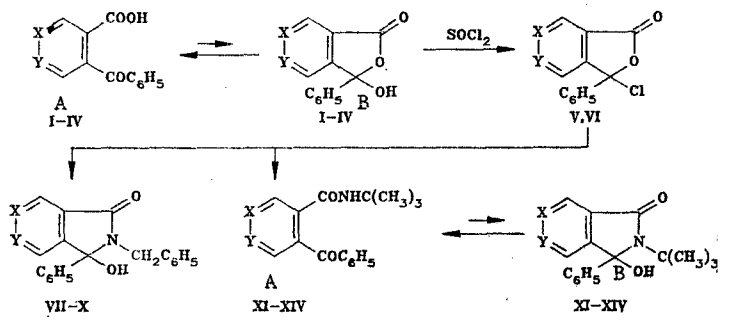
R. É. Valter, and A. É. Batse, and M. V. Petrova

UDC 541.62:547.824'826.1'298.1

4-Benzoylnicotinoyl and 3-benzoylisonicotinoyl chlorides have been found to exist in cyclic forms (3-chloro-3-phenyl-6(or 5)-azaphthalides), and their benzylamides also occur as the cyclic forms (azaisoindolinones). The tert-butylamides of both acids are obtained in the open amide forms. It has been shown by PMR that N-tert-butyl-4-benzoylnicotinamide displays a greater tendency to undergo closure of the isoindolinone ring (K_T = 0.24 in CD_3OD) than does N-tert-butyl-3-benzoylisonicotinamide (K_T = 0).

Ring-chain isomerism in 2-acylbenzoic acids has been the subject of thorough study [1], but in the case of heterocyclic o-carboxylic acids this phenomenon has received little attention [2].

The object of this investigation was to synthesize and examine the ring-chain isomeric interconversions of N-monosubstituted 4-benzoylnicotinamides and 3-benzoylisonicotinamides, and of their protonated forms. According to their IR spectra, both acids (I, III) resemble 2-aroylbenzoic acids [1] in the crystalline state, whereas in solution in dioxane they exist in the open (ketocarboxylic) forms.



I, VII, XI X=N; II, V, VIII, XII X=N+H Cl⁻; III, IV, VI, IX, X, XIII, XIV X=CH; I, II, V, VII, VIII, XI, XII Y=CH; III, VI, IX, XIII Y=N; IV, X, XIV Y=N+HCl⁻

Their hydrochlorides (II, IV) also possess the open structure, although in the IR spectrum of 3-benzoylisonicotinic acid hydrochloride (IV) there is weak absorption at 1805 cm^{-1}, indicating the presence of small amounts of the lactol form (IVB).

Treatment of the acids (I) and (III) with thionyl chloride affords the acid chlorides, which exist in the cyclic chlorolactone form (V, VI), which is also characteristic of 2-acylbenzoyl chlorides [1]. This is confirmed by the presence in their IR spectra of one, and only one C=O band at ~1800 cm^{-1}. The chlorolactone (V) was isolated as its hydrochloride, and (VI) as the free base.

Acylation of benzylamine with the chlorolactones (V) and (VI) gave the cyclic isomeric amides (2-benzyl-3-hydroxy-3-phenyl-6-(or 5)-azaindolinones VII and IX), the IR spectra of which showed broad OH absorption typical of intermolecularly associated hydroxyl groups (O–H...O=C or O–H...N) together with C=O absorption for the isoindolinone at 1703-1685 cm^{-1} (in Nujol). On passing from the crystalline state to the dioxane solution, there is a characteristic shift in this absorption towards higher frequencies as a result of fission of the

A. Ya. Pel'she Polytechnic Institute, Riga 226355. Translated from Khimiya Gererotsiklicheskikh Soedinenii, No. 1, pp. 80-83, January, 1986. Original article submitted November 23, 1984.

0009-3122/86/2201-0067$12.50

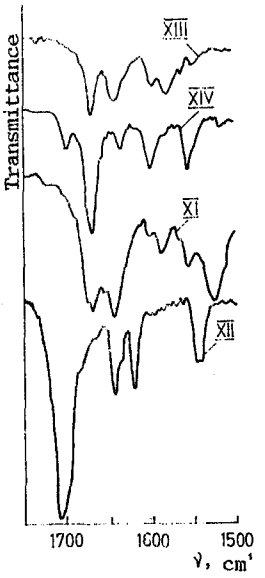


Fig. 1. IR spectra of crystalline N-tert-butylamides and their hydrochlorides.

O–H...O=C hydrogen bonds. The cyclic isoindolinone structure is retained in their hydrochlorides (VIII, X).

It is known [3] that cyclization of 2-acylbenzamides is prevented by the presence of a tert-alkyl substituent on the nitrogen atom, and it has now been found that acylation of tert-butylamine by the chlorolactones (V) and (VI) affords the N-tert-butylamides (XI) and (XIII). Their IR spectra, obtained in Nujol, show absorption for N–H, C=O, amide-I, and amide-II. In the spectra obtained in dioxane solution, the absorption for the ketone C=O and amide-I overlap, and a single band is seen at 1670 cm^{-1}. This, together with the presence of the amide-II band, confirms the open structure of amides (XI) and (XIII) in dioxane solution.

The PMR spectrum of the amide (XI), obtained in CD_3OD, shows two signals for the protons of the tert-butyl group (δ = 1.12, form A, and 1.43 ppm, form B), which is characteristic of the ring-chain equilibrium XIA $\rightleftarrows$ XIB [4]. The ratio of intensities gives the equilibrium constant, K_T = [XIB]/[XIA] = 0.24. In the PMR spectrum of the amide (XIII), there is only one signal for the tert-butyl group at 1.13 ppm, confirming that this amide exists only in the open form (XIIIA) in solution in CD_3OD, within the limits of sensitivity of the PMR method.

The same capacity to exist in the cyclic form is also seen in the crystalling hydrochlorides (XII) and (XIV). The IR spectrum of the hydrochloride (XIV), over the range 1800-1480 cm^{-1}, differs little from that of the base (XIII). The appearance of a low-intensity band at 1698 cm^{-1} (Fig. 1) could be due to the presence of small amounts of the protonated cyclic form (XIVB). The IR spectrum of the hydrochloride (XII) shows a strong, broad band for the isoindolinone C=C at 1707 cm^{-1}, and generally speaking the spectrum at 1800-1480 and 3600-2400 cm^{-1} is similar to that of 2-benzyl-3-hydroxy-3-phenyl-6-azaindolinone (VIII), thus confirming the cyclic structure of 2-tert-butyl-3-hydroxy-3-phenyl-6-azaindolinone hydrochloride (XIIB).

It has thus been shown, taking the N-tert-butylamides as examples, that 4-benzolnicotinamide shows a greater tendency to exist in cyclic forms as a result of intramolecular addition of the amide N–H to the C=O bond than does 3-benzoylisonicotinamide. This behavior also holds true for the hydrochlorides.

EXPERIMENTAL

IR spectra were obtained on IKS-14A and Specord 75-IR instruments, as suspensions in Nujol and as solutions in dioxane (c = $(2.5\text{-}5)\cdot10^{-2}$ mole). PMR spectra were obtained on a Tesla BS-487C (80 MHz) in solution in CD_3OD at 25°C.

4-Benzolnicotinic acid (I) was obtained as described in [5], mp 215-219°C. IR spectrum (Nujol): 2400 (broad band, COOH), 1706 (COOH), 1669 (C=O), 1592, 1577, 1552; (dioxane): 1721 (COOH), 1680 (C=O), 1595, 1581, 1551 cm^{-1}.

Hydrochloride (II). To a solution of 0.1 g of the acid (I) in 2 ml of anhydrous dioxane was added 5 ml of ether saturated with dry hydrogen chloride. There was obtained 0.1 g (86%) of colorless cyrstals, mp 238-242°C (decomposed) IR spectrum (Nujol): 3353, 3282, 3097, 2955, 2858, 2727 br. 2578 br., 2457 br., 1805, 1721, 1680, 1634, 1595 cm^{-1}. Found: Cl 13.0%. $C_{13}H_{10}ClNO_3$. Calculated: Cl 13.4%.

3-Benzoylisonicotinic acid (III) was obtained as described in [5], mp 272°C (decomposed). IR spectrum (Nujol): 2417 (br., COOH), 1722 (COOH), 1670 (C=O), 1594, 1563; (dioxane): 1730 (COOH), 1676 (C=O), 1595, 1580, 1551 cm^{-1}.

Hydrochloride (IV) was obtained similarly to the above. IR spectrum (Nujol): 3369 br., 3098, 3071, 2690, 2580, 2352 br., 1722, 1677, 1635, 1588, 1507 cm^{-1}. Found: Cl 13.0%. $C_{13}H_{10}ClNO_3$. Calculated: Cl 13.4%.

3-Chloro-3-phenyl-6-azaphthalide Hydrochloride (V). A solution of 0.46 g (2 mmole) of the acid (I) and 1.4 ml (20 mmole) of thionyl chloride in 15 ml of benzene was boiled for 4 h. After 24 h, 0.51 g (90%) of colorless crystals of (V) were isolated, mp 171-173°C (decomposed). IR spectrum (Nujol): 3095, 3066, 2869 br., 1814 (C=O), 1644, 1606, 1506 cm^{-1}. Found: Cl 24.6%. $C_{13}H_9Cl_2NO_2$. Calculated: Cl 25.1%.

3-Chloro-3-phenyl-5-azaphthalide (VI) was obtained as in the foregoing example, mp 174-176°C. IR spectrum (Nujol): 3044, 3017, 2698, 2931, 1799 (C=O), 1618, 1549 cm^{-1}. Found: Cl 14.90%. $C_{13}H_8ClNO_2$. Calculated: Cl 14.43%.

2-Benzyl-3-hydroxy-3-phenyl-6-azaindolinone (VII). The hydrochloride (V) (2.5 mmole) was suspended in 10 ml of dioxane, and added to a solution of 2.5 mmole of benzylamine and 5 mmole of triethylamine in 5 ml of dioxane. The mixture was kept for 12 h at 20°C, then diluted with 100 ml of water, the solution saturated with sodium chloride, and 0.74 g (94%) of (VII) isolated, mp 183°C. Two recrystallizations from ethanol gave 0.36 g (46%) of colorless crystals, mp 205-206°C. IR spectrum (Nujol): 3390, 3057 br., 2920, 2830 br., 1703 (C=O), 1609; (dioxane): 1711 (C=O), 1603, 1409 cm^{-1}. Found: C 76.1; H 5.3; N 90%. $C_{20}H_{16}N_2O_2$. Calculated: C 75.9; H 5.1; N 8.9%.

Compounds (IX), (XI), and (XIII) were obtained similarly from the chlorophthalides (V) for (XI) and (VI) for (IX and XIII), and benzylamine for (IX) or tert-butylamine for (XI) and (XIII with the addition of triethylamine.

Hydrochloride (VIII). To a solution of 0.14 g of the isoindolinone (VII) in 2.5 ml of dioxane was added 15 ml of ether saturated with dry hydrogen chloride. There was obtained 0.16 g (100%) of colorless cyrstals of the hydrochloride (VIII), mp. 234-236°C (decomposed). IR spectrum (Nujol): 3412 br., 3051, 2584 br., 1716 (C=O), 1646, 1613, 1536 cm^{-1}. Found: C 69.3; H 5.1; Cl 10.3; N 8.0%. $C_{20}H_{17}ClN_2O_2$. Calculated: C 68.1; H 4.9; Cl 10.0; N 7.9%.

Hydrochlorides (X), (XII), and (XIV) were obtained similarly.

2-Benzyl-3-hydroxy-3-phenyl-5-azaindolinone (IX). Yield 94%, mp 95-98°C. After threefold recrystallization from benzene–hexane, mp 103-106°C (decomposed). IR spectrum (Nujol): 3410 br., 3357 pl., 3157 br., 3067 sh., 2845, 1685 (C=O), 1591; (dioxane): 1714 (C=O), 1590 cm^{-1}. Found: C 75.3; H 5.1; N 8.3%: $C_{20}H_{16}N_2O_2$: Calculated: C 75.9; H 5.1; N 8.9%.

Hydrochloride (X). Mp 220-222°C (decomposed). IR spectrum (Nujol): 3352 br., 3126, 3080, 3030, 2483 br., 1720 sh., 1706 (C=O), 1619 cm^{-1}. Found: C 67.9; H 4.6; Cl 10.9; N 8.0%. $C_{20}H_{17}ClN_2O_2$. Calculated: C 68.1; H 4.9%; Cl 10.0; N 7.9%.

N-tert-Butyl-4-benzoylnicotinamide (XI). After two recrystallizations from benzene–hexane, yield 36%, mp 119-120°C. IR spectrum (Nujol): 3269 (N–H), 3068, 2979, 1674 (C=O), 1632 (amide-I), 1596, 1581, 1556 (amide-II); (dioxane): 1671 (C=O + amide-I), 1594, 1581, 1552, 1531 cm^{-1} (amide-II). Found: C 71.7; H 6.8; N 9.9%. $C_{17}H_{18}N_2O_2$. Calculated: C 72.3; H 6.4; N 9.9%.

Hydrochloride (XII). Mp 224°C (decomposed). IR spectrum (Nujol): 3393, 3100, 3058, 2954, 2508 br., 1707 (C=O), 1643, 1619, 1543 cm^{-1}. Found: C 64.1; H 6.0; Cl 11.4; N 8.7%. $C_{17}H_{19}ClN_2O_2$. Calculated: C 64.0; H 6.0; Cl 11.1; N 8.8%.

N-tert-Butyl-3-benzoylisonicotinamide (XIII). After two recrystallizations from benzene–hexane, yield 56%, mp 110-111°C. IR spectrum (Nujol): 3390 (N–H), 3211 (N–H), 3066, 3043, 2989, 2968, 2931, 2902, 1671 (C=O), 1642 (amide-I, 1593, 1578, 1544 (amide-II); (dioxane): 1668 (C=O + amide-I), 1594, 1579, 1540 sh., 1529 cm^{-1} (amide-II). Found: C 71.6; H 6.6; N 10.0%. $C_{17}H_{18}N_2O_2$. Calculated: C 72.3; H 6.4; N 9.9%.

Hydrochloride (XIV). Mp 220-222°C (decomposed). IR spectrum (Nujol): 3361 (O–H), 3096 (N–H), 3062, 2976, 2923, 2501 br., 1698 (isoindolinone C=O), 1668 (C=O + amide-I), 1657 sh., 1634, 1595, 1551 cm^{-1} (amide-II). Found: C 63.8; H 6.2; Cl 11.3; N 8.7%. $C_{17}H_{19}ClN_2O_2$. Calculated: C 64.0; H 6.0; Cl 11.1; N 8.8%.

LITERATURE CITED

1. R. É. Valter, Ring-Chain Isomerism in Organic Chemistry [in Rusdian], Zinatne, Riga (1978).
2. B. Paul and B. Korytnyk, J. Heterocyc. Chem., 13, 701 (1976).
3. G. A. Karlivan, R. É. Valter, and S. P. Valter, Zh. Org. Khim., 13, 805 (1977).
4. R. B. Kampare, R. É. Valter, É. É. Liepin'sh, and G. A. Karlivan, Izv. Akad. Nauk. Latv. SSR, Ser. Khim., No. 2, 244 (1981).
5. A. A. Artamonov, T. Shneider, and N. V. Baranova, Khim. Geterotsikl. Soedin., No. 4, 514 (1980).

ACETALS OF LACTAMS AND ACID AMIDES.

46.* UNUSUAL REACTIONS OF α-CYANO-β-DIMETHYLAMINOCROTONAMIDE WITH ANTHRANILIC ACID DERIVATIVES

N. Z. Yalysheva, V. V. Chistyakov, and V. G. Granik

UDC 547.391.3'398.1'583.5'856.1'831:543.51'422

It has been shown that the reaction of the enaminoamide α-cyano-β-dimethylaminocrotonamide with anthranilic acid and its ethyl ester unexpectedly gives quinazoline-2,4-dione and 2-methyl-3-cyano-4-quinolone, respectively. The structures of the products were confirmed by their spectra and by direct synthesis.

It has been shown [2] that tertiary enaminoamides react with aromatic amines, the transamination being best effected in acetic acid. For this reason, it was attempted to carry out this reaction with α-cyano-β-dimethylaminocrotonamide (I) and ethyl anthranilate (II) in order to obtain the secondary N-arylenemonoamide (III), which has a functional substituent (the ethoxycarbonyl group) in the ortho-position in the benzene ring. The product obtained was the compound (IV), the mass spectrum of which contained three main peaks†, viz., the molecular peak (162), 119 $(M - CONH)^+$, and 92. The IR spectrum of the compound showed absorption at 1670 and 1700 cm^{-1} (CO), 3160 and 3250 cm^{-1} (NH). These findings, together with the elemental analysis, lead to the conclusion that the reaction of (I) and (II) follows an unexpected route to give quinazoline-2,4-dione (IV). The structure of (IV) was confirmed by comparison with an authentic sample synthesized by a literature method [3].

*For communication 45, see [1].

†Here and subsequently, the m/z values for the peaks are given (with the intensity relative to the maximum ion peak, %, in parentheses.

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow 119021.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 84-87, January, 1986. Original article submitted November 27, 1984.

0009-3122/86/2201-0070$12.50