lowed to react at room temperature for 1 week; the reaction mixture was separated essentially as described in detail for reaction of 1 with **2c** (n = 3). About 20% of the acetylanthranil units were recovered as o-acetamidobenzoic acid (mp 185–186 °C) and the rest was isolated as N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) (mp 179–180 °C). The assigned structure was verified by its IR spectrum and by its NE (calcd 274; obsd 277).

Another solution of 1 (5 g) and **2c** (n = 5) in pyridine (40 cm^3) was allowed to react at room temperature overnight. During this time the quinazolone product separated as a white powder (4.8 g; mp 169–171 °C), which was removed by filtration. The mother liquor was evaporated to dryness at 60 °C (10 mmHg). The nonvolatile semisolid residue was leached with water to remove pyridine. The IR spectrum of the crystalline residue (3.1 g; mp 172–175 °C) was essentially the same as that fraction melting at 169–171 °C (no depression in melting point with a mixed sample). The two fractions were combined and recrystallized from hot water to give N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) in the form of white crystals (7.3 g; 179–180 °C). The IR spectrum of this sample was identical to that obtained via reaction in acetic acid.

Registry No.—**1**, 525-76-8; **2c** (n = 3), 56-12-2; **2c** (n = 5), 60-32-2; o-acetamidobenzoic acid, 89-52-1.

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Acylanthranils. 8. Question of Newman Steric Hindrance in the Reaction of Linear Aliphatic Amines with Acetylanthranil[1]

L. A. Errede* and G. V. D. Tiers

Central Research Laboratories, 3M Company, Saint Paul, Minnesota 55101

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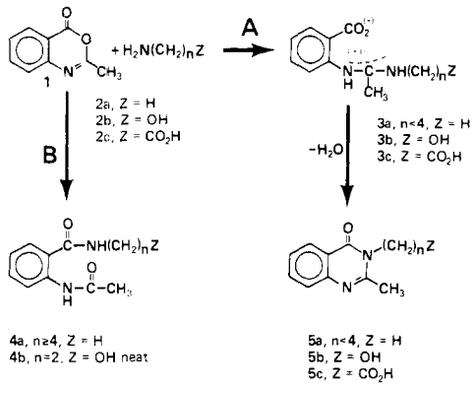
Although hydrocarbon amines with the general formula $H_2N(CH_2)_4R$ (**2**) react "abnormally" with acetylanthranil (**1**) to give the corresponding o-acetamidobenzamide (**4**), analogous amines that do not have a hydrogen atom at the critical fourth carbon position removed from the amino group react "normally" with **1** to give the corresponding acetamidine salt **3**. These results support the premise that the "abnormal" selectivity is caused by the aminotetramethylene segment, which forms a six-membered Newman coil due to intramolecular van der Waals attraction of hydrogen for nitrogen.

It was reported[2,3] that the reaction selectivity of acetylanthranil with the linear aliphatic amines $H_2N(CH_2)_nH$ is dependent upon the number of methylene groups in the aliphatic chain. When $n < 3$ the reaction follows pathway A exclusively to give the corresponding acetamidine intermediate **3** or its cyclodehydration product **5**, but when $n > 3$ the reaction follows pathway B exclusively to give the corresponding o-acetamidobenzamide (**4**) as shown in Scheme I. Reaction with n-propylamine (**2a**) (n = 3) follows both pathways in the relative ratio of A/B > 17/1.

Since pathway B is associated with amines that exhibit steric hindrance to reaction with other electrophiles, whereas pathway A is associated with amines that do not,[4] it was suggested[3] that steric hindrance is also responsible for the sharp crossover in reaction selectivity with **1** at n = 4, and it was postulated further that this steric hindrance is caused by the $H_2N(CH_2)_4$– segment, which is held in the form of a six-membered ring by the small force of intramolecular association of the van der Waals type[3] as shown in Figure 1. Such a configuration is similar to that proposed by Newman[5] in his "Rule of Six" to explain the observed marked decrease in rate of saponification for amides and esters of aliphatic acids with more than three carbon atoms in the chain.

Scheme I



Support of this point of view is found in the observation[6] that the long-chain aliphatic amines $H_2N(CH_2)_nOH$ (**2b**) and $H_2N(CH_2)_nCO_2H$ (**2c**) react with **1** via pathway A, showing that interaction with **1** occurs without steric hindrance, when the long-chain amine has a polar group in the ω position. This remote control by the polar substituent, OH or CO_2H, on the reaction selectivity of the NH_2 group at the other extremity is attributed to the intermolecular hydrogen bonding, especially in a polar solvent, which serves to overcome the weak force of intramolecular van der Waals association that supports the Newman coil. Thus, the ω-substituted amine is kept in a more open configuration, which enables interaction to occur with **1** via pathway A as described previously.[6] Analogous results were obtained[7] with anthranilic acid (**2d**) and with ethanolamine (**2b**) (n = 2). In nonpolar solvents, or neat, these amines interacted with **1** via pathway B, owing to intramolecular hydrogen bonding that formed six- and five-membered rings, respectively. In polar solvents, such as pyridine or acetic acid, however, these amines interacted with **1** via pathway A, since the ring structure that imparted steric hindrance in the

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Table I. Product Distributions Obtained in the Reaction of 1 with H_2NR in Diethyl Ether

Amine	Registry no.	R	% 1 units isolated as 4	3	5	Selectivity at rt A/B = (3 and/or 5)/4
2a ($n < 3$)		$(CH_2)_nH$	0	*a*	0	>50/1[a]
2a ($n = 3$)		$(CH_2)_3H$	*a*	*a*	0	>17/1[a]
2a ($n > 3$)		$(CH_2)_4(CH_2)_{n-1}H$	*a*	0	0	<1/24[a]
2b ($n = 6$)		$(CH_2)_6OH$	0	0	*b*	>50/1[b]
2c ($n = 5$)		$(CH_2)_5CO_2H$	0	0	*b*	>50/1[b]
2e	919-30-2	$(CH_2)_3Si(OEt)_3$	0	95	0	>50/1
2f	65452-64-4	$(CH_2)_3Si[OSi(OCH_3)_3]_3$	16[c]	0	80[c]	~5/1[c]
2g	78-81-9	$CH_2CH(CH_3)_2$	*d*	*d*	0	23/1[d]
2h	5813-64-9	$CH_2C(CH_3)_3$	*d*	*d*	0	12/1[d]
2i ($n = 2$)	753-90-2	CH_2CF_3	0	99	0	>50/1
2i ($n = 3$)	422-03-7	$CH_2CF_2CF_3$	0	0	95	>50/1
2i ($n = 6$)	355-34-0	$CH_2(CF_2)_4CF_3$	0	0	99	>50/1
2j	5332-73-0	$CH_2CH_2CH_2OCH_3$	40[c]	0	40[c]	~1/1[c]
2k	109-85-3	$CH_2CH_2OCH_3$	50[c]	0	25[c]	~1/2[c]

[a] Data taken from ref 2. [b] Data taken from ref 3. [c] Product mixture isolated as an oil. The product distribution (i.e., selectivity) was estimated from its IR and NMR spectra. [d] Data taken from ref 5.

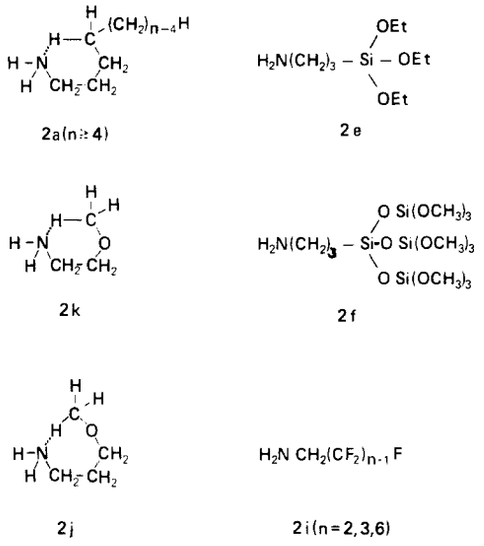

Figure 1.

nonpolar solvents now was precluded by intermolecular hydrogen bonding at the extremities.

A similar mitigating effect of a polar group in the ω position on the chemistry of long-chain aliphatic amines is evidenced when one compares the reactions of the amines $H_2N(CH_2)_nH$[3] and $H_2N(CH_2)_nOH$[7] with hydronium ions in aqueous solution. The pK_a values of the amines $H_2N(CH_2)_nH$ as a function of n show a maximum[3] of 10.81 at $n = 2$ followed by a smooth decrease to the line 10.62 ± 0.03 for all values of $n > 3$, whereas the pK_a values for the amines $H_2N(CH_2)_nOH$ show no such maximum[8] but rather increase monotonically from 5.96 at $n = 0$ to 10.62 at $n = 6$.

Although these results are consistent with the postulation that the change in chemistry as a function of n is caused by the formation of a Newman coil as shown in Figure 1, they do not implicate specifically intramolecular van der Waals attraction of the nitrogen atom with a hydrogen atom on the fourth methylene group. A more definitive test of this hypothesis is the product distribution obtained when acetylanthranil is made to react with similar long-chain aliphatic amines that have no hydrogen atom in this critical position. If this hypothesis is correct then the product distribution obtained with these amines will indicate that reaction occurs predominantly via pathway A instead of B despite the fact that these amines may have rather bulky substituents elsewhere than at the α-carbon atom.

A few amines of this type were available to us for testing with acetylanthranil. Accordingly, the respective material balances were completed as described previously[4,9] and the corresponding reaction selectivities calculated therefrom are collected in Table I for easy comparison with results obtained in earlier studies. The corresponding characterization data of new products and derivatives thereof are collected in Table II.

The data show that triethoxy-3-amino-*n*-propylsilane (**2e**), which has oxygen atoms in each of the three critical positions, as shown in Figure 1, follows pathway A instead of B to give the corresponding acetamidine salt intermediate **3e** in 95% yield, despite the fact that the $-Si(OEt)_3$ group in the fourth position is bulkier than a $-CH_3$ group, which caused reaction with *n*-butylamine to follow pathway B exclusively.

A sample of **3e** was converted in good yield to the corresponding quinazolone **5e** by fusion above 100 °C to confirm the assigned structure.

Even the amine, tris(trimethylsilyloxy)-3-amino-*n*-propylsilane (**2f**) favored pathway A over pathway B in the ratio of about 5/1, despite the enormous umbrella-like bulk of the $-Si[OSi(OCH_3)_3]_3$ group in the fourth position. In this case the product mixture was isolated as an oil that could not be separated chemically owing to the hydrolytic instability of the trimethylsilyloxy group. The IR and NMR spectra of this oil, however, indicated that cyclodehydration of **3f** had occurred to give the corresponding quinazolone **5f** and that the ratio of **5f** to **4f**, the *o*-acetamidobenzamide product obtained via pathway B, was 5/1.

These results indicated that an H atom located on the fourth carbon position removed from the amino group is virtually a necessary condition for "abnormal" reaction of linear aliphatic amines with acetylanthranil via pathway B, while mere bulkiness has relatively little effect, unless of course it is on N itself or the α-carbon atom as reported previously.[4] Similar results were noted earlier with C_4 and C_5 amines; both isobutyl- and neopentylamines[4] (**2g** and **2h**), which have no fourth carbon position, followed A preferentially, whereas the corresponding straight chain C_4 and C_5 amines followed pathway B despite their relative less "bulky" geometry.

To test the six-ring hypothesis further, acetylanthranil was allowed to react with a set of fluorocarbon amines of generic formula $H_2NCH_2(CF_2)_nF$ (**2i**). These have no H atom at the critical fourth carbon position for ring formation and consequently should not exhibit the crossover in selectivity with increase in chain length.

Table II. Characterization Data for Products 3, 4, and 5 Listed in Table I

Product	Mp, °C	Key IR abs bands in μm	NMR[b] data (Me_2SO-d_6) in τ values
Acetamidines, 3			
From amine **2g**	78–83	2.9–4.0, 6.1, 6.3, 6.5	
From amine **2i** (n = 2)	107–8	3.2–4.3 6.1, 6.3, 6.5	
2-Methylquinazolones, 5			
From **3g**	185–200	6.0, 6.3	
From **3i** (n = 2)	92–3	6.0, 6.3	
From **2i** (n = 3)	106–7	6.0, 6.3	
From **2i** (n = 6)	100–2	6.0, 6.3	1.7–2.5 (cpx, Ar), 4.86 (t, CH_2N), 7.33 (s, CH_3)
From **2k**	72–4[a]	6.0, 6.3	
2-Acetamidobenzamides, 4			
From **2k**	83–5[a]	3.1, 6.1, 6.2, 6.3, 6.5	−1.2 and 1.3 (2, NH), 1.4–2.9 (cpx, Ar)
From **3i** (n = 2) (trace)	191–194	3.1, 6.1, 6.3, 6.5	6.49 (cpx, $NHCH_2CH_2O$), 6.69 (s, CH_3O), 7.84 (s, $CH_3C{=}O$)

[a] Isolated from the product mixture obtained as an oil by repeated recrystallization from hexane and manual separation of two distinctly different crystalline types to give small samples of **5k** and **4k** for identification purposes. [b] cpx = complex, t = triplet, s = singlet.

The data are summarized in Tables I and II. The results obtained with the first two members of this set (i.e., 1,1-dihydroperfluoroethylamine (**2i**) (n = 2) and 1,1-dihydroperfluoro-n-propylamine (**2i**) (n = 3)) showed that fluorocarbon amines with less than four carbon atoms react like their hydrocarbon counterparts to give the corresponding acetamidine salt **3** via pathway A, but at a slower rate owing to the decreased basicity of the amine. Significantly, no crossover in selectivity was noted when 1,1-dihydroperfluoro-n-hexylamine (**2i**) (n = 6) was made to react with **1**. The "normal" pathway was followed and the correspoinding quinazolone **5i** (n = 6) was isolated in good yield as the only product of the reaction.

One might expect to find borderline cases that manifest intermediate selectivity when gross structural changes modify the ability of the molecule to form or hold the coiled structure illustrated with **2a**. One such change is replacement of a methylene group by an ether link.

Acetylanthranil was allowed to react with the amino ether $H_2N(CH_2)_3OCH_3$ (**2j**) which lacks a hydrogen atom in the "critical" fourth position. A product mixture of **5j** and **4j** was obtained which indicated that reaction occurred via both pathways at comparable rates. While the analogous five ring would seem untenable due to the six-bond oppositions required, a seven-membered ring analogous to the coil form of **2a** would not suffer from that objection, though perhaps it would be partially destabilized by entropy effects related to ring size and the flexibility of the ether link. Some support for this view is provided by results with the lower amino ether $H_2N(CH_2)_2OCH_3$ (**2k**) for which was found only a small preference for the "abnormal" pathway B. This is consistent with the above suggestion but not decisive.

Taken as a whole these results support the premise[2,3] that aliphatic hydrocarbon amines with the segment $H_2N(CH_2)_4$–, which can form a coiled six-membered configuration by intramolecular association, do indeed exhibit Newman "Rule-of-Six" steric hindrance to reaction with electrophilic reagents.

Experimental Section

General Procedure. Acetylanthranil was allowed to react at ca. 25 °C with an equivalent amount of a chosen amine in diethyl ether and the products were separated according to the scheme described in detail in a previous publication.[9] Samples of the acetamidine salt **3** when isolated were converted to the corresponding quinazolone **5** by fusion or by solution in dilute aqueous base as described previously.[10] The percentage of acetylanthranil units isolated as the products **3**, **4**, and **5** and the corresponding reaction selectivities, **A/B** = (**3** and/or **5**)/**4**, calculated therefrom are collected in Table I. The characterization data for the products isolated in these reactions and the quinazolones produced by cyclodehydration of the acetamidines isolated are collected in Table II.

Amines Used. Tri(ethoxy)-3-aminopropylsilane (**2e**) was obtained as a commercial sample "A-1100" from Union Carbide Corp. Tris-(trimethylsilyloxy)-3-aminopropylsilane (**2f**) was obtained from D. N. Vivona of the 3M Co., who had prepared the amine from **2e**. His preparation is described in a recent patent.[11] The fluorocarbon amine, 1,1-dihydroperfluoroethylamine (**2i**) (n = 2), was obtained from Dr. T. S. Reid of the 3M Co., who prepared the compound by reduction of perfluoroacetonitrile according to the procedure of Bissel and Finger;[12] 1,1-dihydroperfluoro-n-propylamine (**2i**) (n = 3) was prepared by Dr. D. R. Husted (now deceased) of the 3M Co., according to the procedure of Husted and Ahlbrecht;[13] 1,1-dihydroperfluoro-n-hexylamine (**2i**) (n = 6) was synthesized by M. L. Sandberg of the 3M Co. via catalytic reduction of perfluoro-n-hexanonitrile according to the procedure of Husted and Ahlbrecht.[14] The amino ethers, 3-methoxy-n-propylamine (**2j**) and 2-methoxyethylamine (**2k**), were from American Cyanamid Co. and Eastman Organic Chemicals Co., respectively.

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Registry No.—**1**, 525-76-8; **3g**, 34264-52-3; **3i** (n = 2), 65452-65-5; **4i** (n = 2), 65452-71-3; **4k**, 65452-70-2; **5g**, 391-03-7; **5i** (n = 2), 65452-66-6; **5i** (n = 3), 65452-67-7; **5i** (n = 6), 65452-68-8; **5k**, 65452-69-9.

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