Antibacterial Activity of *N*-(β-Styryl)formamides Related to Tuberin[1]

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A series of para-substituted *N*-(β-styryl)formamides, analogues of tuberin (**4a**), has been prepared and assayed for antibacterial activity. The methylthio, ethoxy, and methyl analogues **4e**, **4j**, and **4t** were about twice as active as tuberin against *Mycobacterium phlei*. Although tuberin lacks activity against *Staphylococcus aureus*, several of the analogues described were found to inhibit this organism. The phenyl group of tuberin is not a prerequisite for activity since analogues based on naphthyl or ferrocenyl groups were also active. A quantitative structure–activity relationship further implied that an aromatic group need not be present, suggesting the synthesis of the cyclohexyl and *n*-amyl analogues which were found to possess high activity.

The growth of various species of mycobacteria is inhibited by the weak antibiotic tuberin although other bacteria are unaffected.[2] We have synthesized a series of analogues, some of which show activity greater than that of tuberin against mycobacteria, while others are also active against *Staphylococcus aureus*.

Chemistry. The required *N*-(β-styryl)formamides **4a**–**t** were prepared from the cinnamic acids **1a**–**t** as shown in Scheme I.[3] The same methods were also applicable to the preparation of the furyl, thienyl, 2-naphthyl, 1-naphthyl, ferrocenyl, cyclohexyl, and *n*-amyl analogues **5a**–**g**.

Results and Discussion

A group of six analogues, **4a**–**f**, covering a wide range of substituent π, π^2, $\mathcal{F}$, and $\mathcal{R}$, was selected from a list of candidates, using the determinant (X'X) criteria,[4] for initial synthesis and screening against *Mycobacterium phlei*. The resulting minimum inhibitory concentrations (MIC), when plotted in the π–σ biological activity coordinate system as described by Darvas,[5] showed an apparent correlation. Further compounds were then prepared leading to the data displayed in Figure 1 and Table I. Maximum activity about two times that of tuberin (**4a**, R = MeO) was obtained in a small region enclosing the EtO, Me, and MeS substituents. Values of the MIC against *M. phlei* and *S. aureus* are listed in Table I. Significant activity against *S. aureus* was observed for several of the compounds, in contrast to the inactivity of tuberin.

From the graphical structure–activity correlation it was clear that compounds with more than two to three times the activity of tuberin were unlikely to be obtained from para-substituted *N*-(β-styryl)formamides. This was confirmed by a quantitative structure–activity (QSAR) relation (see below). Compounds with major modifications of the aromatic system were therefore prepared. The most active of these, the 2-naphthyl analogue **5c**, had about four times the activity of tuberin against *M. phlei*. The ferrocenyl analogue **5e** had an MIC equal to that of tuberin (see Table II).

The observation that large changes in the aromatic system did not necessarily impair activity, and the results of a QSAR study, suggested that the aromatic portion of tuberin was not a requirement. This was confirmed by the preparation of the cyclohexyl and *n*-amyl analogues **5f**,**g** which were found to be about one-half and two times as potent as tuberin.

QSAR Studies. Table III gives the relevant data for QSAR studies. Lipophilicities were determined by three procedures (the interrelations are more fully discussed in ref 6): (a) classical shake-flask, (b) LC on C18 Corasil using 25 wt % MeOH/pH 7.0 buffer, and (c) LC on C18 Corasil coated with 1-octanol using pH 7.0 buffer saturated with 1-octanol. Shake-flask and the new C18 Corasil/octanol procedures gave excellent agreement (correlation coefficient 0.99); however, C18 Corasil/25 wt % MeOH showed systematic deviations due to hydrogen-bonding substituents. If $D_{ha} = 1$ for hydrogen-bonding acceptors and $D_{ha} = 0$ for non-hydrogen-bonding substituents, then we obtain eq 1 relating log P and log k'. All terms are significant at

$$\log P = 1.7\ (\pm 0.2) + 1.2\ (\pm 0.2) \log k' - 0.3\ (\pm 0.2)\ D_{ha} \quad (1)$$
$$n = 19;\ r = 0.973;\ s = 0.161;\ F_{2,16} = 140$$

the 95% confidence limits or better; n = number of points, s = standard deviation of points from the line, r = correlation coefficient, F is the overall significance parameter, and 95% confidence limits are given in parentheses. As shown in eq 2, the log P values are not those of substituted

$$\log P = 1.9\ (\pm 0.2) + 0.98\ (\pm 0.13)\ \pi_{benzene} + 0.3\ (\pm 0.4)\ \mathcal{F} \quad (2)$$
$$n = 19;\ r = 0.977;\ s = 0.143;\ F = 166$$

benzenes but deviate[8] because of the electronegative formamide group. (The $\mathcal{F}$ term is significant at the 90% confidence limits.) Note that $\pi_{benzene}$ was used in the initial planning, but this should have only a minor effect on the overall design, the main purpose of which was to obtain a spread in substituent types.

The resulting QSAR using log k' and log P are given in eq 3–5 where pA = log $1/MIC_M$. The unsubstituted

$$pA = -0.3\ (\pm 1.4) + 2.9\ (\pm 1.1) \log P - 0.5\ (\pm 0.2)\ (\log P)^2 - 2.6\ (\pm 0.9)\ \mathcal{F}^2 - 1.7\ (\pm 0.5)\ \mathcal{R}^2 + 0.4\ (\pm 0.3)\ D_{ha} \quad (3a)$$
$$n = 19;\ r = 0.952;\ s = 0.161;\ F_{5,13} = 25$$

$$pA = -1.1\ (\pm 2.4) + 3.1\ (\pm 1.9) \log P - 0.5\ (\pm 0.4)\ (\log P)^2 - 1.8\ (\pm 1.5)\ \mathcal{F}^2 - 1.6\ (\pm 0.9)\ \mathcal{R}^2 + 0.5\ (\pm 0.5)\ D_{ha} \quad (3b)$$
$$n = 20;\ r = 0.856;\ s = 0.283;\ F_{5,14} = 8$$

$$pA = 3.1\ (\pm 0.5) + 1.2\ (\pm 1.0) \log k' - 0.6\ (\pm 0.5)\ (\log k')^2 - 2.1\ (\pm 1.4)\ \mathcal{F}^2 - 1.1\ (\pm 0.7)\ \mathcal{R}^2 \quad (4)$$
$$n = 18;\ r = 0.867;\ s = 0.257;\ F_{4,13} = 10$$

$$pA = 3.4\ (\pm 0.3) + 0.8\ (\pm 0.3)\ \pi_{benzene} - 0.4\ (\pm 0.2)\ \pi^2_{benzene} - 2.2\ (\pm 1.0)\ \mathcal{F}^2 - 1.6\ (\pm 0.6)\ \mathcal{R}^2 + 0.4\ (\pm 0.3)\ D_{ha} \quad (5)$$
$$n = 19;\ r = 0.943;\ s = 0.175;\ F_{5,13} = 21$$

compound **4c** was omitted because of very large deviations of the observed activity from calculated values in all equations examined. (See, for example, eq 3b where **4c** deviates by 2.6 standard deviations and the quality of the correlation is considerably reduced by including this point.) Since **4c** is the only para-unsubstituted compound,

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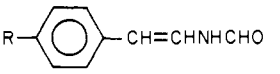
Table I. Physical Data and Antibacterial Activity of Tuberin Analogues



No.	R	Mp or bp (mm), °C	Recrystn solvent	Formula[a]	MIC, μg/mL *M. phlei*	MIC, μg/mL *S. aureus*
4a	CH_3O	135–136	Me_2CO-hexane	(Tuberin)	80	*b*
4b	NO_2	128–130	EtOAc-hexane	$C_9H_8N_2O_3$	320	3
4c	H	100–101	C_6H_6	C_9H_9NO	640	50
4d	*t*-Bu	98–99	C_6H_6	$C_{13}H_{17}NO$	80	200
4e	MeS	130–131	EtOAc	$C_{10}H_{11}NOS$	40	100
4f	Me_2N	158–160	EtOAc	$C_{11}H_{14}N_2O$	640	*b*
4g	Et_2N	150 (0.05)		$C_{13}H_{18}N_2O$	320	*b*
4h	HO	197–198	Me_2CO	$C_9H_9NO_2$	*c*	*b*
4i	AcO	112	EtOAc	$C_{11}H_{11}NO_3$	640	*b*
4j	EtO	114–115	EtOAc	$C_{11}H_{13}NO_2$	40	*b*
4k	*i*-PrO	92–93	EtOAc-hexane	$C_{12}H_{15}NO_2$	320	*b*
4l	*n*-BuO	110–111	EtOAc-hexane	$C_{13}H_{17}NO_2$	80	*b*
4m	F	75–76	EtOAc	C_9H_8FNO	160	*b*
4n	Cl	90–92	EtOAc	C_9H_8ClNO	80	200
4o	Br	95–96	EtOAc-hexane	C_9H_8BrNO	160	100
4p	I	128–129	EtOAc-hexane	C_9H_8INO	160	200
4q	F_3C	103–105	Me_2CO-hexane	$C_{10}H_8F_3NO$	80	100
4r	CN	127, 141[d]	Me_2CO-hexane	$C_{10}H_8N_2O$	640	*b*
4s	$PhSO_2$	138–140	EtOAc	$C_{15}H_{13}NO_3S$	320	*b*
4t	Me	124–125	C_6H_6	$C_{10}H_{11}NO$	40	*b*

[a] Analyzed for C, H, and N. [b] Inactive at 200 μg/mL. [c] Inactive at 640 μg/mL. [d] Double melting point.

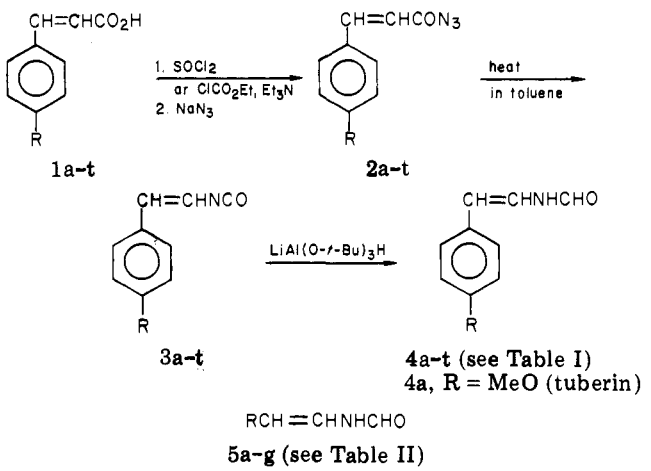
Table II. Physical Data and Antibacterial Activity of Tuberin Analogues

RCH=CHNHCHO

No.	R	Mp, °C	Recrystn solvent	Formula[a]	MIC, μg/mL *M. phlei*	MIC, μg/mL *S. aureus*
5a	2-Furyl	109–110	EtOAc-hexane	$C_7H_7NO_2$	*c*	*b*
5b	2-Thienyl	85–86	C_6H_6	C_7H_7NOS	320	25
5c	2-Naphthyl	157	Me_2CO-hexane	$C_{13}H_{11}NO$	20	*b*
5d	1-Naphthyl	137–138	EtOAc-hexane	$C_{13}H_{11}NO$	80	*b*
5e	Ferrocenyl	128–130	$CHCl_3$-hexane	$C_{13}H_{13}FeNO$	80	200
5f	Cyclohexyl	*d*		$C_9H_{15}NO$	160	*b*
5g	*n*-Amyl	*d*		$C_8H_{15}NO$	40	*b*

[a–c] See corresponding footnotes in Table I. [d] Gum.

Scheme I



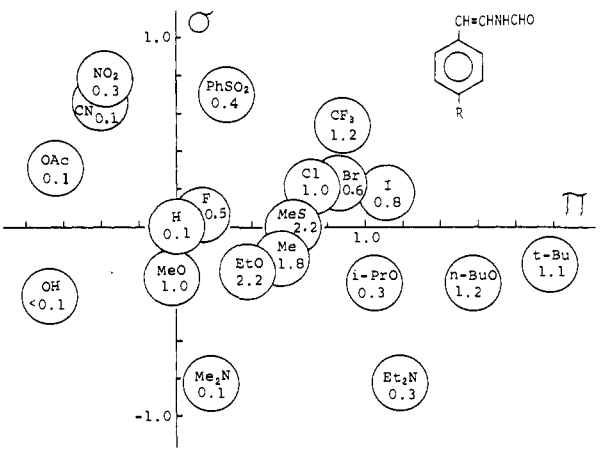


Figure 1. Antibacterial activities of tuberin analogues in the π–σ coordinate system. Substituent R and activity (molar basis) against *Mycobacterium phlei*, relative to tuberin, are shown.

metabolic deactivation is a possible cause. Equations 3–5 were obtained by searching all regressions of log k' (or log P), (log k')^2 [or (log P)^2], $\mathcal{F}$, $\mathcal{F}^2$, $\mathcal{R}$, $\mathcal{R}^2$, MR, D_{ha}, and the cross product (log k')D_{ha} [or (log P)D_{ha}]. Note that there are only 18 log k' values (Table III), since **4c** is omitted and **4g** could not be measured due to lack of compound. All terms are significant at the 95% confidence limits by t tests, and no terms with statistical significance can be added to these equations. Log P and (log P)^2 terms [and log k' and (log k')^2] are highly correlated because of the small range; using RIDGE regression,[9] which can deconvolute this interrelation, we find the same optimal log P_0 and log k_0, however.

The following conclusions can be drawn. (1) The optimum electronic effect occurs with electronically *neutral* substituents since there is no linear term in $\mathcal{F}$ or $\mathcal{R}$ (the same is true if σ_p is used in place of $\mathcal{F}$ and $\mathcal{R}$). This observation suggested the preparation of cyclohexyl and *n*-amyl analogues. (2) Log P_0 = 2.87 (2.7–3.13, 95%

Table III. Data for QSAR Study on 4-X-PhCH=CHNHCHO Tuberin Analogues

X	pA_{obsd}[a]	pA_{calcd}[b]	Log k'[c]	Log P[d]	$\pi_{benzene}$[e]	σ_p[e]	$\mathcal{F}$[e]	$\mathcal{R}$[e]	D_{ha}[f]
3,4-$(CH)_4$	3.99	3.80	1.16[g]	3.22	1.32	0.04	0.03	0.01	0
OEt	3.68	3.61	0.65	2.31	0.38	−0.24	0.22	−0.44	1
SMe	3.68	3.65	0.77	2.55	0.61	0.00	0.20	−0.18	0
Me	3.60	3.74	0.66	2.45	0.56	−0.17	−0.04	−0.13	0
O-*n*-Bu	3.44	3.45	1.62[g]	3.32[h]	1.33[i,j]	−0.32	0.25	−0.55	1
CF_3	3.43	3.41	1.09	3.06	0.88	0.54	0.38	0.19	0
t-Bu	3.40	3.36	1.71[g]	3.82[h]	1.98	−0.20	−0.07	−0.13	0
Cl	3.36	3.37	0.79	2.70	0.71	0.23	0.41	−0.15	0
OMe	3.34	3.16	0.28	1.94[k]	−0.02	−0.27	0.26	−0.51	1
I	3.23	3.33	1.14	3.18	1.12	0.18	0.40	−0.19	0
Br	3.15	3.31	0.96	2.87	0.86	0.23	0.44	−0.17	0
F	3.01	2.89	0.33	2.11	0.14	0.06	0.43	−0.34	0
SO_2Ph	2.95	2.92	0.78	1.95	0.27	0.70	0.56	0.18	1
NEt_2	2.83	2.81	*j*	2.90	1.18	−0.90	0.01	−0.91	1
O-*i*-Pr	2.81	3.07	0.93[g]	2.61	0.36	−0.45	0.30	−0.72	1
NO_2	2.78	2.57	0.24	1.94	−0.28	0.78	0.67	0.16	1
OAc	2.51	2.55	0.16	1.32[k]	−0.64	0.31	0.41	−0.07	1
NMe_2	2.47	2.39	0.48	2.03	0.18	−0.83	0.10	−0.92	1
CN	2.43	2.69	0.04	1.62[k]	−0.57	0.66	0.51	0.19	1
H	2.36	3.42[j]	0.21	1.95[k]	0.00	0.00	0.00	0.00	0

[a] Log $1/MIC_{molar}$ vs. *M. phlei*. [b] From eq 3a. [c] C18 Corasil/25 wt % MeOH/pH 7.00 phosphate buffer (0.001 M) or as noted. $k' = (t_x - t_0)/t_0$ where t_x is the retention time of compound and t_0 is for the unretained compound. [d] C18 Corasil/octanol/pH 7.00 phosphate buffer (0.01 M); see ref 6. [e] Pomona College Medicinal Chemistry Project or see ref 7. [f] D_{ha} = 1 if H-bond acceptor. [g] Determined in 40 wt % MeOH and extrapolated to 25 wt % by log $k'_{25} = 0.825 + 1.169 \log k'_{40}$ ($n = 4$; $r = 0.990$) which was established for $D_{ha} = 0$ substituents. OEt was found to be +0.05 higher than calculated and this increment was added to O-*n*-Bu and O-*i*-Pr (i.e., assume parallel lines with displacement due to H bonding). [h] For $D_{ha} = 0$, $\log P = 1.68 + 1.25 \log k'$ ($n = 9$; $r = 0.994$), which is used for *t*-Bu, while for OR substituents $\log P = 1.65 + 1.03 \log k'$ ($n = 3$; $r = 1.0$), which is used for O-*n*-Bu. [i] From $\pi = -1.79 + 0.968 \log P - 0.382\,\mathcal{F}$ ($n = 19$; $r = 0.979$; $s = 0.143$; reverse of eq 2). [j] H omitted from eq 3–5; NEt_2 omitted from eq 1 and 4 (not determined); O-*n*-Bu omitted from eq 2, unreliable literature value. [k] Log *P* by shake-flask: X = H, 1.93 (±0.01); X = OMe, 1.92 (±0.02); X = CN, 1.58 (±0.01); X = OAc, 1.40 (±0.01). The estimated standard deviation by interpolation using standards is 0.03.

confidence limits). Note that log *P* for the cyclohexyl and *n*-amyl analogues **5f** and **5g** is 2.69 and 2.65, respectively. (3) The origin of the D_{ha} term is interesting. If it were present in eq 3 because of an activity enhancing effect, the term would be expected to appear in eq 4, but it cannot be added with statistical significance. Substitution of eq 1 in eq 3 should give rise to a cross-product term (log k')D_{ha}; however, this term also cannot be added to eq 4. This suggests that alkane (log k') may be a better model for the waxy[10] mycobacteria than octanol (log *P*). The D_{ha} term in eq 3 and 5 "corrects" octanol back toward a purer alkane phase. The high activity of the cyclohexyl and *n*-amyl analogues tends to support the view that D_{ha} represents a correction of the lipophilicity scale rather than a special activating effect. (4) Finally, eq 2 and 3a can be used to calculate a MIC of 1133 μg/mL for the inactive 4-OH compound **4h** which was excluded from the QSAR. This further confirms the above QSAR.

A QSAR study of substituted phenyl 4-aminosalicylates vs. *M. tuberculosis* and *M. bovis* has appeared;[11] however, while electronic effects were found to be important, the mode of action of these compounds probably differs from that of the tuberins. The same may also be true of a study of 3-benzoylacrylic acids vs. *M. tuberculosis* H37Rv where an electronic term improved the correlation.[12] The Hammett ρ value for this term was negative, in contrast to a positive ρ value found in the case of 2,6-dialkoxyphenylpenicillins,[13] which, it was argued,[12] showed potential structural similarities in part. Optimal electronic effects have been found, for example, in a study of acaricidal hydrazones.[14]

The optimal log $P_0 = 2.87$ for tuberins vs. *M. phlei* is far from the general log P_0 found for relatively nonspecific agents (ca. 4 for gram-negative and 6 for gram-positive bacteria[15]); however, it is close to the log *P* found for some of the more lipophilic penicillins, such as dicloxacillin (log *P* = 2.83 and 2.45).

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are corrected. Standard agar dilution methods (in duplicate) were used for the determination of MIC values vs. *M. phlei* (estimated standard deviation less than 0.15 log units) and microdilution methods (in triplicate) for *S. aureus* (estimated standard deviation less than 0.3 log units). QSAR regressions were performed on the Proprietary Computer Systems, Inc., APL system. Literature log *P* values were from Hansch et al.[7] or the Pomona College Medicinal Chemistry Project.

Synthesis of *N*-(β-Styryl)formamides. Compounds **4a**–e and **4i**–t were synthesized via the acid chloride according to Scheme I, following experimental procedures previously described.[3] Compounds **4f** and **4g** were prepared via the mixed anhydride according to Scheme I.

***N*-(*p*-Hydroxy-β-styryl)formamide (4h).** A mixture of *N*-(*p*-acetoxy-β-styryl)formamide (**4i**) (200 mg, 1.03 mmol) in 3 mL of Me_2SO was added to a stirred suspension of Fleischmann's yeast (2 g) in 55 mL of 10% phosphate buffer at 42 °C. After 18 h the mixture was extracted with ether and the ethereal solution dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from acetone gave **4h** (149 mg, 95%).

Partition Coefficients. Procedures are described in ref 6. For the shake-flask procedure, both phases were analyzed and quadruplicates were run. Log k' values were determined with reference to 25 wt % MeOH by linear regression from 40 wt % MeOH for the more lipophilic compounds ($r = 0.990$) with non-hydrogen-bonding substituents. Hydrogen-bonding substituents showed different sensitivities to solvent change and were placed on the 25 wt % scale, if they could not be measured directly, by appropriate corrections using overlapping series.

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References and Notes

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Syntheses and Uncoupling Activities of Alkyl Dithiocarbazates and Alkyl Pyridinecarbonyldithiocarbazates

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A series of alkyl dithiocarbazates, alkyl 3-picolinoyldithiocarbazates, alkyl 3-nicotinoyldithiocarbazates, alkyl 3-isonicotinoyldithiocarbazates, and alkyl 3-picolinoyl-2-methyldithiocarbazates was prepared. These alkyl pyridinecarbonyldithiocarbazates were shown to be uncouplers of oxidative phosphorylation in mitochondria. The finding that uncoupling activity increased with increase in the length of the alkyl chains of the compounds indicates that hydrophobicity influences the activity. The nonyl derivatives had the highest activity. The results also suggested that a dissociable acidic proton is necessary for the uncoupling activity.

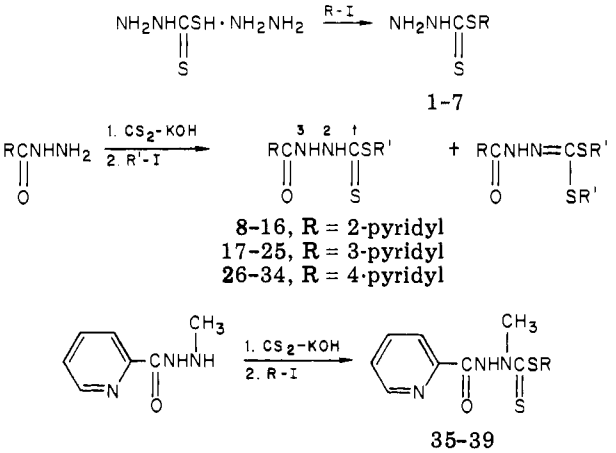
Various biologically active substances, such as antibacterial, antifungal, and nonsteroidal antiinflammatory agents, are known to be inhibitors or uncouplers of oxidative phosphorylation in mitochondria.[1] Thus in vitro experiments on the effects of various compounds on mitochondrial function may be a good way to find new series of biologically active reagents,[1c] although it is still uncertain whether mitochondria are directly involved in the site of action of these reagents. Recently, Bäuerlein and Keihl reported that nonylthiourea and nonylthiouracil effectively released the respiration of mitochondria.[2]

The alkyl 3-picolinoyldithiocarbazates reported previously,[3] **8–14**, have the same thiocarbamoyl structure as that in thiourea and thiouracil. Thus our recent finding (unpublished data) that they showed uncoupling activity prompted us to examine the effects of the complete series of alkyl dithiocarbazates **1–7** and alkyl pyridinecarbonyldithiocarbazates **8–34** on oxidative phosphorylation in mitochondria. Most uncouplers have a dissociable proton and an important role of this proton in the uncoupling has been stressed extensively.[4] Since the NH proton adjacent to the C=S group of the dithiocarbazates is expected to be dissociable, we synthesized the N^2-methylated alkyl 3-picolinoyldithiocarbazates **35–39** in order to examine the role of the acidic proton in the uncoupling action of this series of uncoupler.

Chemistry. Methyl[5] and ethyl dithiocarbazate[6] are already known. Attempts to prepare higher esters than *n*-propyl esters were reported to be unsuccessful,[7] but we obtained the higher esters **1–7** from *n*-propyl to *n*-nonyl ester in good yields by treating aqueous ethanolic solutions of the hydrazinium dithiocarbazates with alkyl iodides at room temperature and extracting the products with benzene (Scheme I).

The syntheses of methyl and ethyl pyridinecarbonyldithiocarbazates **8**, **9**, **17**, **18**, **26**, and **27** by reaction of

Scheme I



potassium dithiocarbazates with alkyl iodides have been reported previously.[3,8] However, higher alkyl esters than propyl pyridinecarbonyldithiocarbazates could not be obtained by the procedure used for syntheses of the methyl and ethyl esters. Previously, we obtained alkyl 3-picolinoyldithiocarbazates **10–14** by adding alkyl iodides to a mixture of acid hydrazides, carbon disulfide, and potassium hydroxide in ethanol.[3]

In the present study, compounds **8–34** were prepared by the latter procedure. Reinvestigation of the latter procedure revealed that, even using an equimolar amount of alkyl iodide, large amounts of the *S,S'*-dialkyl derivatives were formed in addition to the desired *S*-alkyl derivatives **8–34**. Although *S,S'*-dimethyldithiocarbonate picolinoylhydrazone and *S,S'*-dimethyldithiocarbonate isonicotinoylhydrazone were obtained as crystals, the other *S,S'*-dialkyl derivatives were isolated as oily products that could not be obtained in analytically pure form. Five alkyl

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