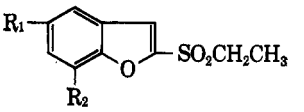
TABLE II

2-ETHYLSULFONYLBENZOFURANS

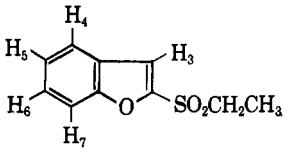


R_1	R_2	M.p., °C.	Yield, %	Formula	Calcd., % C	H	S	X	Found, % C	H	S	X
H	H	91–92	59.5	$C_{10}H_{10}O_3S$	57.1	4.79	15.2		57.2	4.87	15.0	
Cl	H	123–124	54	$C_{10}H_9ClO_3S$	49.1	3.71	13.0	14.5[a]	49.0	3.87	13.1	14.4[a]
Br	H	113–114	39	$C_{10}H_9BrO_3S$	41.5	3.14	11.1	27.6[b]	41.6	3.22	10.8	27.9[b]
NO_2	H	181–182	22	$C_{10}H_9NO_5S$	47.0	3.55	12.6	5.49[c]	47.3	3.58	13.0	5.22[c]
H	NO_2	187–188	25	$C_{10}H_9NO_5S$	47.0	3.55	12.6	5.49[c]	47.2	3.78	12.3	5.62[c]
Cl	Cl	141–142	62	$C_{10}H_8Cl_2O_3S$	43.0	2.89	11.5	25.4[a]	43.0	2.88	11.2	25.6[a]

[a] Chlorine. [b] Bromine. [c] Nitrogen.

TABLE III

N.M.R. PROPERTIES OF SUBSTITUTED 2-ETHYLSULFONYLBENZOFURANS[a]



Substituent	Chemical shift[b] δ (p.p.m.)[c]	Assignment	Coupling constant, J (c.p.s.)
None	7.94 (s)	H_3	
	7.3 (m)	H_4, H_5, H_6, H_7	
	3.13 (q)	$-CH_2-$	
	1.28 (t)	$-CH_3$	
5-Chloro	8.39 (s)	H_3	
	8.05 (d, d)	H_4	$J_{46} = 1.8$
	7.65 (m)	H_6, H_7	$J_{47} = 0.8$
	3.32 (q)	$-CH_2-$	$J_{67} = 8.2$
	1.39 (t)	$-CH_3$	
5-Bromo	7.99 (s)	H_3	
	7.78 (m)	H_4	
	7.32 (m)	H_6, H_7	$J_{67} = 9.0$
	3.17 (q)	$-CH_2-$	
	1.32 (t)	$-CH_3$	
5-Nitro	8.95 (d)	H_4	$J_{46} = 2.3$
	8.54 (d, d)	H_6	$J_{67} = 9.9$
	8.49 (s)	H_3	
	7.87 (d, d)	H_7	$J_{47} = 0.8$
	3.38 (q)	$-CH_2-$	
	1.43 (t)	$-CH_3$	
7-Nitro	8.54 (s)	H_3	
	8.40 (m)	H_4, H_6	$J_{45} = J_{56} = 8.5$
	7.70 (t)	H_5	
	3.32 (q)	$-CH_2-$	
	1.42 (t)	$-CH_3$	
5,7-Dichloro	8.36 (s)	H_3	
	7.85 (d)	H_4	$J_{46} = 1.9$
	7.55 (d)	H_6	
	3.27 (q)	$-CH_2-$	
	1.38 (t)	$-CH_3$	

[a] Spectra were obtained in deuteriochloroform solution containing internal tetramethylsilane (TMS). A Varian HR-60 high resolution n.m.r. spectrometer operating at 60 Mc./sec. was employed. Spectra were calibrated by the audiofrequency side-band technique [J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951)] utilizing a frequency counter. [b] Referred to internal TMS. [c] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

was 62% when piperidine was employed as the catalyst (Table II).

The use of 0.1 the equimolar amount of piperidine in the cyclization of 3,5-dichlorosalicylaldehyde with **3** resulted in the isolation of 5,7-dichloro-2-ethylsulfonylbenzofuran in only 11.7% yield and the recovery of 55% of unchanged **3**.

Attempts to cyclize 3,5-dichlorosalicylaldehyde employing a small amount of piperidine acetate (10 g./mole of aldehyde) resulted in no detectable reaction and 92% of **3** was recovered unchanged.

Acknowledgment.—We are indebted to Mr. D. R. Beasecker and his staff for the elemental analyses and to Mr. Alan Tharp for assistance in the infrared measurements.

The Addition of Alcohols to Dicyandiamide. A Correction of the Literature

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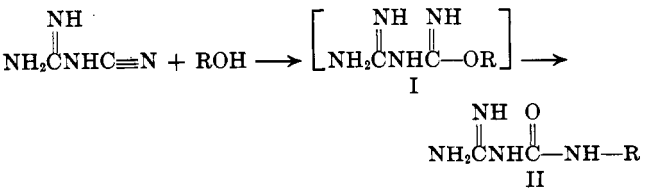
Received August 4, 1964

Among the methods claimed as being useful for the synthesis of 1-amidino-3-alkylureas is the one published by Dutta and Ray.[1] The procedure, as reported, involved the addition of an alcohol to dicyandiamide in the presence of copper acetate. The resulting chelate salt was treated with ammonium sulfate which precipitated the insoluble copper ammonium sulfate salt of the alleged 1-amidino-3-alkylurea. Treatment with hydrogen sulfide produced the free base. The authors suggested that a rearrangement occurred by which the 1-amidino-O-alkylurea originally formed (I) was transformed into the compounds in question (II).



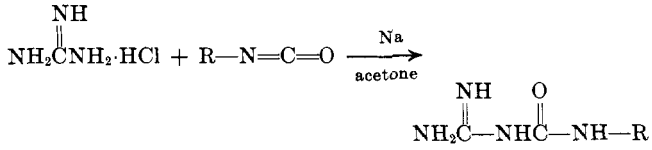
We have now shown unequivocally that the compounds prepared by Dutta and Ray are, in fact, not the 1-amidino-3-alkylureas (II) but rather the O-alkylureas (I).

A search of the literature revealed a method of synthesizing 1-amidino-3-alkylureas (II)[2] which was unambiguous. This method involved the reaction

(1) R. L. Dutta and P. Ray, *J. Indian Chem. Soc.*, **36**, 499 (1959).

(2) F. H. S. Curd, D. G. Davey, and D. N. Richardson, *J. Chem. Soc.*, 1732 (1949).

of guanidine hydrochloride with an isocyanate in the presence of sodium and acetone and yielded the amidinourea as the free base.



We repeated this work with the *n*-butyl and *n*-hexyl homologs, converted each to the sulfate salt, and made a direct comparison of each with the sulfate salt of the corresponding *n*-butyl and *n*-hexyl homologs prepared by the method of Dutta and Ray. From this examination it was obvious that the two procedures yielded entirely different compounds.

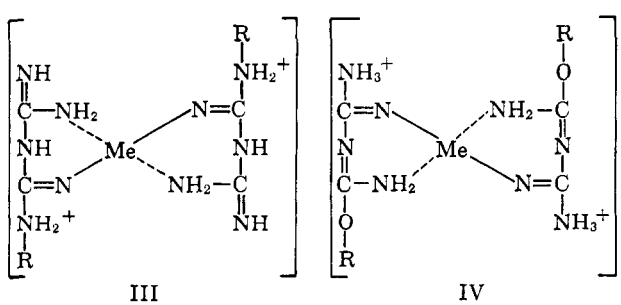
In order to determine further the nature of the compounds produced by Dutta and Ray, we examined the work of Kawano and Odo.[3] Although Kawano and Odo did not cite the work of the Indian workers, they did publish a similar procedure but concluded that the products obtained therefrom were 1-amidino-O-alkylureas which they isolated as the hydrochlorides.

In order to clarify the problem, we prepared 1-amidino-3-O-ethylurea hydrochloride by the method of Kawano and Odo,[4] converted it to the corresponding sulfate, and compared it directly with the product obtained by the method described by Dutta and Ray. The two compounds were identical and showed no mixture melting point depression.

Hence it was concluded from the foregoing experiments that the compounds obtained by the latter workers, from the reaction of alcohols on dicyandiamide, were indeed the 1-amidino-O-alkylureas (I) and not 1-amidino-3-alkylureas (II) as originally claimed.

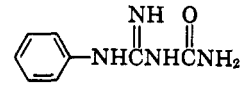
It is of interest to note the difference in ability of the 1-amidino-O-alkylureas (I) to form metal chelates compared with the 1-amidino-3-alkylureas (II). Thus, Dutta and Ray reported that their compounds (which were actually 1-amidino-O-alkylureas) formed metal chelates,[1,5-8] and made use of this fact in their isolation. Our repetition of this work substantiated these observations. In contrast, however, we have found that the 1-amidino-3-alkylureas (II) do not form metal chelates.

Ray and Saha[9] have postulated that biguanides, which readily form metal complexes, have a chelated structure represented by III. An analogous structure (IV) can be assigned to the 1-amidino-3-O-alkylureas.



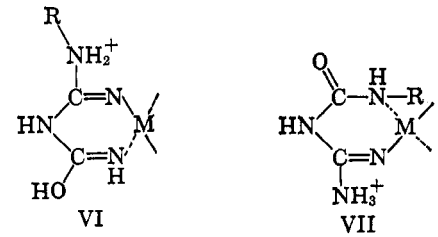
III IV

Kundu and Ray[10,11] observed that 1-amidino-3-phenylurea, which has the phenyl substituent adjacent to the –CO– group, does not form metal complexes. This loss of chelating ability was attributed to the decrease in the basicity of the nitrogen bearing the aryl group. As noted above, however, this inability to form complexes was also observed to be true when an alkyl substituent, such as butyl or hexyl, was in this position. Slotta and Tschesche[12] have made a similar observation in the case of 1-amidino-3-methylurea. On the other hand, when the phenyl group is attached to the nitrogen adjacent to the >C=NH, the complexing power is unhindered. Thus, 1-phenylamidinourea (V) produced a pink precipitate when treated with ammoniacal copper sulfate.



V

It would appear, therefore, that the difference in metal-complexing ability of the 3-amidino-1-substituted ureas is due not to the degree of basicity of these compounds but rather to steric factors operating between the metal and the nitrogen atoms with which it complexes. Thus, 1-substituted-amidino ureas (*e.g.*, V) can contribute two unsubstituted nitrogen atoms for complexing with a metal (*e.g.*, formula VI), whereas 1-amidino-3-substituted ureas have only one unsubstituted nitrogen atom to offer for complexing (*e.g.*, VII). Interference between R and the metal atom in VII could explain the inability of 3-amidino-1-substituted ureas to form metal complexes.[13]



VI VII

Experimental[14]

1-Amidino-O-butylurea Sulfate.—This compound was prepared according to the procedure of Dutta and Ray[1] using 25 g. (0.297 mole) of dicyandiamide, 25 g. of copper acetate, and 300 ml. of *n*-butyl alcohol to give 15 g. of product which, after crystallization from methanol–acetone, melted at 134–136°. This was in agreement with the literature value (137–138°).[1]

1-Amidino-3-butylurea Sulfate.—1-Amidino-3-butylurea was prepared according to the procedure described by Curd[2] using 3.2 g. (0.137 g.-atom) of sodium, 14.3 g. (0.149 mole) of guanidine hydrochloride, and 7.5 g. (0.138 mole) of butyl isocyanate. The free base was not purified but was converted to the sulfate, in the following manner, in order to compare the product directly with the material prepared by Dutta.

An ethereal solution of the crude base was cooled in an ice bath and neutralized by the dropwise addition of sulfuric acid whereupon an oil separated. The ether was decanted, fresh ether was added, and the mixture was cooled. On standing for several days, crystals appeared, yielding 1.5 g., m.p. 180–195°

(3) K. Kawano and K. Odo, *Yuki Gosei Kagaku Kyokai Shi*, **20**, 568 (1962); *Index Chemicus*, **6**, 21383 (1962).
(4) K. Kawano and K. Odo, *J. Chem. Soc. Japan*, **82**, 1672 (1961).
(5) R. L. Dutta and P. Ray, *J. Indian Chem. Soc.*, **36**, 567 (1949).
(6) R. L. Dutta, *ibid.*, **37**, 499, 565, 573, 789 (1960).
(7) P. Ray, *Chem. Rev.*, **61**, 313 (1961).
(8) R. L. Dutta and S. Lahiry, *J. Indian Chem. Soc.*, **38**, 689 (1961).
(9) P. Ray and H. Saha, *ibid.*, **14**, 670 (1937).
(10) N. Kundu and P. Ray, *ibid.*, **29**, 811 (1952).
(11) P. Ray, *ibid.*, **32**, 141 (1955).
(12) K. H. Slotta and R. Tschesche, *Ber.*, **62**, 1390 (1929).
(13) We would like to thank the referee for his suggestions on the clarification of this argument.
(14) All melting points, unless otherwise specified, are corrected. We are grateful to Mr. K. D. Fleischer and staff for analytical services.

(uncor.). After several recrystallizations from methanol–ether, an analytical sample was obtained, m.p. 197–198°.

Anal. Calcd. for $C_6H_{14}N_4O \cdot 0.5H_2SO_4$: N, 27.05; S, 7.74. Found: N, 27.09; S, 7.92.

This material produced a melting point depression when mixed with the 1-amidino-O-butylurea sulfate prepared above.

1-Amidino-O-hexylurea Sulfate.—The material obtained by the procedure of Dutta and Ray[1] had a melting point of 132–135°.

1-Amidino-3-hexylurea.—The free base was prepared by the procedure of Curd,[2] m.p. 91–92°. The sulfate was prepared by treatment of a methanolic solution of base with ethereal sulfuric acid until the solution was slightly acidic. The solvent was removed *in vacuo* and the oily residue was dissolved in isopropyl alcohol. The addition of ether precipitated the sulfate, m.p. 128–129° (uncor.). Further recrystallization from isopropyl alcohol–ether raised the melting point to 131–134°.

Anal. Calcd. for $C_8H_{18}N_4O \cdot 0.5H_2SO_4$: C, 40.83; H, 8.14; N, 23.81. Found: C, 41.11; H, 8.09; N, 24.01.

A mixture melting point with the 1-amidino-O-hexylurea sulfate prepared above produced a depression.

1-Amidino-O-ethylurea Sulfate. A.—The compound was prepared by the procedure of Dutta and Ray.[1] As prepared by us it had a melting point of 165–166° which differed from that reported in the literature (137–138°). This experiment was repeated with the same results.

B.—1-Amidino-O-ethylurea hydrochloride was synthesized by the procedure of Kawana,[4] m.p. 162–163° (uncor.), in agreement with the latter workers' melting point. The hydrochloride was converted to the sulfate in the following manner. Amberlite IRA-400 resin (20 g.) was slurried with distilled water, put into a chromatographic column, washed with 2 *N* sulfuric acid until the eluent produced a negative chloride test, and then washed with distilled water to neutrality. 1-Amidino-O-ethylurea hydrochloride (2 g.) was dissolved in 95% ethanol (25 ml.) and passed through the column. Ethanol (100 ml.) was added and the solution was collected and evaporated to yield a white solid which was dissolved in 20 ml. of 95% ethanol. Acetone was added (20 ml.), whereupon a white solid formed, m.p. 166–167°. A mixture melting point with the material obtained by the method of Dutta and Ray[1] showed no depression.

The Rearrangement of 1-Piperidinemethanethiol Esters

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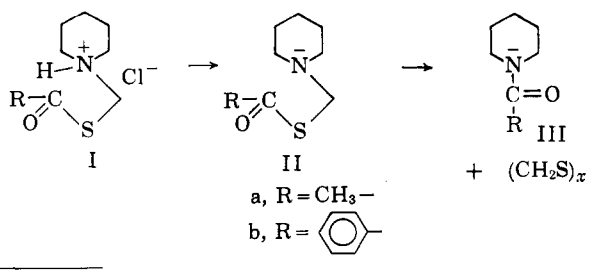
In an attempt to characterize a compound believed to be the hydrochloride salt of 1-piperidinemethanethiol acetate (Ia) it was converted to the free base (IIa). On distillation a clear liquid was obtained which gave an incorrect analysis for the desired product. An investigation of the nuclear magnetic resonance (n.m.r.) and infrared spectra of the distillate indicated the product to be 1-acetylpiperidine (IIIa). This was confirmed by comparison with an authentic sample.



I II III

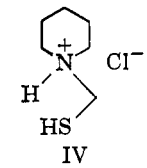
a, R = CH_3–

b, R =

+ $(CH_2S)_x$

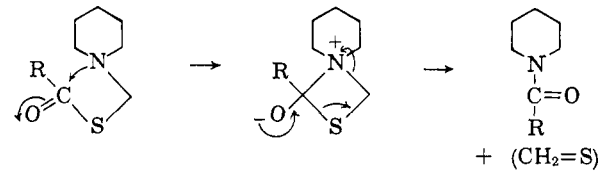
(1) National Institutes of Health Predoctoral Fellow, 1963–1964.

To expand on this study a convenient synthesis for the acetyl and benzoyl esters Ia and Ib from 1-piperidinemethanethiol hydrochloride (IV) was devised. The parent compound, IV, prepared by the method of Binz and Pence,[2] was heated with the corresponding thiolcarboxylic acid to afford the desired compound and hydrogen sulfide.



IV

The rearrangement of the thiol esters was effected by refluxing the free base in benzene. A plausible explanation for this facile rearrangement can be depicted as follows.



+ $(CH_2=S)$

Experimental[3]

1-Piperidinemethanethiol Acetate Hydrochloride (Ia).—To 16.7 g. (0.1 mole) of 1-piperidinemethanethiol hydrochloride (IV) was added 55.0 g. (0.72 mole) of thiolacetic acid and the mixture was heated at steam-bath temperature for 3 hr. The reaction mixture was allowed to cool and then added to 500 ml. of anhydrous ether. The resulting precipitate was collected and washed twice with ether. The white solid was recrystallized from absolute alcohol to give 16.4 g. (79%) of the desired compound: m.p. 169° dec.; $\lambda_{C=O}^{CHCl_3}$ 5.85 μ; n.m.r. 150 (s, $-CH_3$), 269 (s, NCH_2S), 197 (m, NCH_2), and 104 (m, CCH_2) c.p.s. in D_2O.

Anal. Calcd. for $C_8H_{16}ClNOS$: C, 45.82; H, 7.68; N, 6.67; S, 15.29. Found: C, 45.90; H, 7.42; N, 6.78; S, 14.78.

1-Piperidinemethanethiol Benzoate Hydrochloride (Ib).—A suspension of 10.0 g. (0.06 mole) 1-piperidinemethanethiol hydrochloride (IV) and 25.0 g. (0.18 mole) of thiolbenzoic acid in 50 ml. of dichloromethane was heated at steam-bath temperature for 1.5 hr. The dichloromethane was removed and the residue was poured into 500 ml. of anhydrous ether. The resulting precipitate was collected and redissolved in a minimum amount of dichloromethane. This solution was dropped slowly into 250 ml. of anhydrous ether. After repeating this procedure three times, 10.2 g. (63%) of the desired material, a crystalline solid, m.p. 158° dec., was obtained. Decomposition of this material occurred somewhat during the purification procedure with enough impurity being formed to prohibit an accurate elemental analysis. The structure was established by spectral comparison with 1-piperidinemethanethiol acetate hydrochloride (Ia). Ib showed $\lambda_{C=O}^{CHCl_3}$ 5.95 μ; n.m.r. 477 and 484 (d, *ortho* =CH—), 456 (m, *meta* and *para* =CH—), 288 (s, NCH_2S), 190 (m, NCH_2), and 117 (m, CCH_2) c.p.s. in $DCCl_3$.

1-Piperidinemethanethiol Acetate (IIa) and 1-Piperidinemethanethiol Benzoate (IIb).—Aqueous solutions of 1-piperidinemethanethiol acetate hydrochloride (Ia) and 1-piperidinemethanethiol benzoate hydrochloride (Ib) were made basic with saturated sodium bicarbonate solution. These solutions were then extracted with ether and the extracts were dried over anhydrous magnesium sulfate. The ether was removed *in vacuo* without the use of heat; the free bases were examined by n.m.r. and infra-

(2) A. Binz and L. H. Pence, *J. Am. Chem. Soc.*, **61**, 3134 (1939).

(3) Melting points were obtained on a calibrated Kofler micro hot stage and a Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR5 and IR8 spectrophotometers. Nuclear magnetic resonance data were recorded on a Varian Associates Model A-60 spectrophotometer using TMS as the internal standard. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England.