4-Bromo-3,4-dihydro-6,7-methylenedioxyisocoumarin (Vd).—After refluxing for 1 hr. a mixture of IVd (0.54 g.), N-bromosuccinimide (0.54 g.), and benzoyl peroxide (0.005 g.) in carbon tetrachloride (15 ml.), benzoyl peroxide (0.005 g.) was again added and the reflux continued for 2 hr. The mixture worked up as detailed above for the preparation of Vc. Recrystallizations of the product from ethyl acetate–petroleum ether (ice chest) yielded Vd in rosettes of needles (0.5 g.; 65%), m.p. 129°.

Anal. Calcd. for $C_{10}H_7O_4Br$: C, 44.2; H, 2.6; Br, 29.5. Found: C, 44.5; H, 3.0; Br, 29.8.

6,7-Methylenedioxideisocoumarin (VId).—Dehydrobromination of Vd (0.2 g.) with triethylamine (5 ml.), according to the procedure described above for the preparation of VIc, gave the product which on vacuum sublimation (bath temp., 150°/0.8 mm.) yielded white sublimate. Recrystallizations from ethyl acetate followed by methanol furnished pure VIc in rectangular prisms (0.1 g.; 71%), m.p. 168–169°.

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.15; H, 3.16. Found: C, 63.13; H, 3.42.

Acknowledgment.—We thankfully acknowledge the award of a University Grants Commission research scholarship to one of us (J.N.S.).

A New Synthesis of Ureas. IV. The Preparation of Unsymmetrical Ureas from Carbon Monoxide, Sulfur, and Amines

R. A. FRANZ,[1] FRED APPLEGATH,[1] F. V. MORRISS,[2]
FRED BAIOCCHI,[2] AND L. W. BREED[2]

Laboratories of the Hydrocarbons Division of the Monsanto Chemical Company, St. Louis, Missouri, and Midwest Research Institute, Kansas City 10, Missouri

Received June 25, 1962

The possible preparation of unsymmetrical ureas by the reaction of carbon monoxide, sulfur, and mixtures of amines has been investigated. The procedure may be most successfully used in the synthesis of 1,1-dialkyl-3-arylureas, and a series of these compounds was prepared and characterized.

An extension of a new method for the synthesis of urea from ammonia, carbon monoxide, and sulfur[3] to the preparation of symmetrical disubstituted ureas in high yields from aliphatic and aromatic amines was described recently.[4,5] The same procedure has proved to be satisfactory for the preparation of 1,1-dialkyl-3-arylureas, but is less advantageous for other classes of unsymmetrical ureas.

On the basis of experimental evidence, a mechanism has been proposed for the formation of urea from carbon monoxide, sulfur, and ammonia which involves the following steps[3]: initial formation of carbonyl sulfide from carbon monoxide and sulfur; condensation of carbonyl sulfide with ammonia to yield ammonium thiolcarbamate; decomposition of ammonium thiolcarbamate to cyanic acid and ammonium bisulfide; and the subsequent condensation of cyanic acid with ammonia to give urea. The recent isolation of thiolcarbamates from the reaction of dialkylamines with carbon monoxide and sulfur offers additional evidence for this mechanism.[6] If a mixture of two amines, for example, a primary and a secondary amine, were substituted for ammonia, the process could be represented by the following sequence:

$$S + CO \rightleftharpoons COS \tag{1}$$

$$R_2NH + COS \rightleftharpoons R_2NCOSH\cdot R_2NH \tag{2}$$

$$RNH_2 + COS \rightleftharpoons RNHCOSH\cdot RNH_2 \rightleftharpoons RNCO + RNH_2\cdot H_2S \tag{3}$$

$$RNCO + RNH_2 \rightleftharpoons RNHCONHR \tag{4}$$

$$RNCO + R_2NH \rightleftharpoons R_2NCONHR \tag{5}$$

Because in this case the isocyanate intermediate can only be produced from the primary amine used in the reaction mixture, the possible urea products are the symmetrical disubstituted urea formed in (4) and the unsymmetrical trisubstituted urea obtained in (5). At the temperatures used in these syntheses, the equilibria in (4) and (5) favor the urea; therefore, the proportions of the two ureas in the product will be determined by the relative rates of reactions 4 and 5. The yield of the trisubstituted urea will be expected to be influenced by the nucleophilic character of the secondary amine, in comparison to that of the primary amine, and the presence or absence of steric hindrance in the secondary amine.

The situation becomes more complicated in the preparation of monosubstituted ureas when the mixed amines are a primary amine and ammonia. Both an organo isocyanate and cyanic acid may be considered as intermediates, each competing for the two amines. Attempts to prepare monosubstituted ureas from primary amines, ammonia, sulfur, and carbon monoxide led to mixtures containing the three possible products. Some of these results are summarized in Table I.

---

[1] Monsanto Chemical Co.

[2] Midwest Research Institute.

[3] R. A. Franz and F. Applegath, *J. Org. Chem.*, **26**, 3304 (1961).

[4] R. A. Franz, F. Applegath, F. V. Morriss, and F. Baiocchi, *ibid.*, **26**, 3306 (1961).

[5] R. A. Franz, F. Applegath, F. V. Morriss, F. Baiocchi, and C. Bolze, *ibid.*, **26**, 3309 (1961).

[6] D. W. Grisley, Jr., and J. A. Stephens, *ibid.*, **26**, 3568 (1961).

TABLE I

PREPARATION OF MONOSUBSTITUTED UREAS

$RNH_2 + NH_3 + CO + S \longrightarrow H_2NCONH_2 + RNHCONH_2 + RNHCONHR$

	Yield, %		
RNH_2	H_2NCONH_2	$RNHCONH_2$	RNHCONHR
n-Octylamine	15	51	31
n-Dodecylamine	19	38	25
Aniline	52	0.7	16

Similarly, the use of two primary amines in the reaction would involve the formation of two intermediate organo isocyanates. Attempts to prepare unsymmetrical disubstituted ureas by treating a primary aliphatic amine with a primary aromatic amine in the presence of carbon monoxide and sulfur usually gave a low yield of the desired product, and considerable amounts of the dialkyl or diarylureas were frequently obtained. The quantities of ureas isolated in several of these preparations are summarized in Table II.

TABLE II

PREPARATION OF UNSYMMETRICAL DISUBSTITUTED UREAS

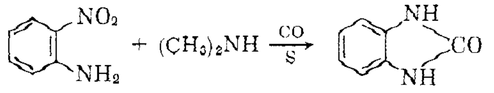
$RNH_2 + R'NH_2 + CO + S \longrightarrow RNHCONHR + RNHCONHR' + R'NHCONHR'$

		Yield, %		
RNH_2	$R'NH_2$	RNHCONHR	RNHCONHR′	R′NHCONHR′
Ethylamine	*p*-Toluidine	..	17	6
n-Propylamine	Aniline	..	10	1
n-Butylamine	*p*-Chloroaniline	70	9	..
n-Butylamine	Aniline	..	37	..
n-Butylamine	*p*-Aminophenol	7	30	60
n-Amylamine	*p*-Aminophenol	20	35	35
n-Octylamine	*p*-Aminophenol	65	39	..
n-Hexylamine	N,N-Dimethyl-*p*-phenylenediamine	69	..	..
n-Octylamine	N,N-Dimethyl-*p*-phenylenediamine	62	..	..

Attempts to prepare trisubstituted ureas by this procedure gave results that correlated well with the mechanism postulated in equations 1–5. In general, the reactants necessary for 1,1-dialkyl-3-arylureas meet the requirements of one amine capable of forming an isocyanate and a second more basic amine incapable of yielding an isocyanate. Good yields of this class of compounds were obtained when a variety of amines were used, and the results are summarized in Table III. Many of the compounds have not been reported in the literature.

Failure to obtain an unsymmetrical urea when aniline was treated with either dicyclohexylamine or di-2-ethylhexylamine in the presence of carbon monoxide and sulfur verified the importance of steric factors in equation 5. It is interesting to see that less favorable yields are obtained and significant quantities of starting materials are recovered when an *o*-substituted aniline derivative is used in the preparation. Therefore, stearic factors must also exert an influence in at least one step of equation 3 or 4.

Table III also demonstrates that many carbon-functional groups do not interfere significantly with the reaction. However, an attempt to prepare 1,1-dimethyl-3-(*p*-nitrophenyl)urea gave a high melting solid that was not the desired urea. It was subsequently shown by the use of *o*-nitroaniline that under the conditions required the nitro group underwent reduction with the formation of benzimidazolinone.[7] Presumably, the product from *o*-nitroaniline was a phenyleneurea polymer. *p*-Aminobenzonitrile also failed to give the desired urea.



It was also found that the same procedure was suitable for the preparation of a series of 1,1-dialkyl-3-arylurea type compounds containing two urea groups.

$$R_2NCONHR'NHCONR_2$$
$$R' = \text{arylene};\ R = \text{alkyl}$$

The properties of this series of compounds, none of which are reported in the literature, are summarized in Table IV.

Other classes of trisubstituted ureas were not so readily prepared in good yields.

When the secondary amine was a very weakly basic amine, only the disubstituted symmetrical urea derived from the primary amine was obtained. Thus, aniline and diphenylamine or aniline and methylphenylamine gave only diphenylurea; *n*-decylamine and methylphenylamine gave only didecylurea.

1,1,3-Trialkylureas were obtained by treating a primary and a secondary aliphatic amine with carbon monoxide and sulfur; however, the symmetrical dialkylurea was usually also formed. Because of the similarity in the basicity of the two amines, competition of the intermediate isocyanate for the two amines became a significant factor, and

---

(7) The reduction of nitro groups by sulfur in basic solution has been reported a number of times in the literature. References to this reaction are summarized by W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., 1962, p. 150.

TABLE III. PROPERTIES AND ANALYSES OF 1,1-DIALKYL-3-ARYLUREAS

Compound	Yield, %	M.p., °C., observed	M.p., °C., reported	Recrystallization solvent	Formula	Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1,1-Dimethyl-3-phenylurea	79	131–132	127–129[a]	H_2O	$C_9H_{12}N_2O$						
1,1-Dimethyl-3-*p*-tolylurea	54	152–153		EtOH	$C_{10}H_{14}N_2O$	67.38	67.05	7.92	7.91	15.72	15.49
							67.29		7.75		15.29
1,1-Dimethyl-3-(2,4-xylyl)urea	81	133–136		$CHCl_3$	$C_{11}H_{16}N_2O$	68.71	68.54	8.38	8.40	14.57	14.15
							68.35		8.32		14.24
1,1-Dimethyl-3-(2,5-xylyl)urea	68	87–88		EtOH	$C_{11}H_{16}N_2O$	68.71	68.85	8.38	8.63	14.57	14.74
							68.77		8.38		14.54
1,1-Dimethyl-3-(2,6-xylyl)urea	40	132–133		EtOH	$C_{11}H_{16}N_2O$	68.71	68.75	8.38	7.34	14.57	14.33
							68.51		8.48		14.25
1,1-Dimethyl-3-(1-naphthyl)urea	78	165–166		MeOH	$C_{13}H_{14}N_2O$	72.87	72.35	6.58	6.57	13.08	12.78
							72.12		6.70		12.78
1,1-Dimethyl-3-(2-naphthyl)urea	92	203–205	210.5–210.8[b]	EtOH	$C_{13}H_{14}N_2O$	72.87	73.00	6.58	6.62	13.08	12.82
							73.29		6.54		12.83
3-(*o*-Chlorophenyl)-1,1-dimethylurea	23	104–106	94.1–95.4[c]	MeOH	$C_9H_{11}ClN_2O$	54.41	54.43	5.58	5.51	14.10	13.80
							54.73		5.57		13.68
3-(*m*-Chlorophenyl)-1,1-dimethylurea	57	144–146	144.3–144.8[d]	EtOH	$C_9H_{11}ClN_2O$	54.41	54.39	5.58	5.62	14.10	13.71
							54.26		5.67		13.84
3-(*p*-Chlorophenyl)-1,1-dimethylurea	86	170–171	170–171[e]	EtOH	$C_9H_{11}ClN_2O$						
3-(3,4-Dichlorophenyl)-1,1-dimethylurea	62	152–154	155[f]	. . .	$C_9H_{10}Cl_2N_2O$	46.37	46.10	4.32	4.18	12.02	11.86
							Cl: Calcd., 30.42.		Found, 30.60		
1,1-Dimethyl-3-(*p*-methoxyphenyl)urea	88	130–132		MeOH–H_2O	$C_{10}H_{14}N_2O_2$	61.83	61.77	7.26	7.41	14.43	14.11
							61.96		7.22		14.21
3-(2,5-Dimethoxyphenyl)-1,1-dimethylurea	19[g]	52–54		MeOH	$C_{11}H_{16}N_2O_3$	58.90	59.09	7.19	7.14	12.49	12.39
							59.27		7.34		12.44
3-(5-Chloro-2-methoxyphenyl)-1,1-dimethylurea	18[h]	63–66		Skellysolve "B"	$C_{10}H_{13}ClN_2O_2$	52.51	52.77	5.73	5.70	12.25	12.02
							52.97		5.84		12.29
1,1-Dimethyl-3-*p*-hydroxyphenylurea	64[i]	194–196		H_2O	$C_9H_{12}N_2O_2$	60.00	60.82	6.67	6.58	15.55	15.62
3-(*p*-Carboxyphenyl)-1,1-dimethylurea	45	214–216		*i*-PrOH	$C_{10}H_{12}N_2O_3$	57.68	57.68	5.81	5.91	13.45	13.08
							57.70		6.00		13.08
3-(*p*-Carbethoxyphenyl)-1,1-dimethylurea	35[j]	144–146		EtOH	$C_{12}H_{16}N_2O_3$	60.90	60.90	6.82	6.85	11.84	11.39
							60.91		6.89		11.47
1,1-Dimethyl-3-(*p*-dimethylaminophenyl)-urea	93	173–174		EtOH	$C_{11}H_{17}N_3O$	63.74	63.46	8.23	8.31	20.28	20.08
							63.46		8.31		20.03
3-(2-Benzothiazolyl)-1,1-dimethylurea	17	214–215	218–220[k]	MeOH	$C_{10}H_{11}N_3OS$	54.27	54.33	5.01	5.17	18.99	18.28
							S: Calcd., 14.49.		Found, 15.02		
1,1-Di-*n*-butyl-3-phenylurea	75	82–83	82.7–83.0[l]	EtOH–H_2O	$C_{15}H_{24}N_2O$	72.53	72.90	9.74	9.76	11.28	11.17
							72.76		9.74		11.19
1,1-Di-*iso*-butyl-3-phenylurea	52	104–106		EtOH	$C_{15}H_{24}N_2O$	72.53	72.51	9.73	9.76	11.28	10.96
							72.61		9.76		11.06
3-(*p*-Chlorophenyl)-1,1-di-*n*-butylurea	39	123	122[m]	C_6H_6	$C_{15}H_{23}ClN_2O$						
3-(*p*-Chlorophenyl)-1,1-diallylurea	10	73–74	80–81[n]	*i*-PrOH	$C_{13}H_{23}ClN_2O$						
4-Morpholinecarboxanilide	50	156–159	161.5–162[o]	MeOH	$C_{11}H_{14}N_2O_2$	68.96	69.24	11.58	11.52	12.37	12.05
4′-Chloro-4-morpholinecarboxanilide	66	196–200	196[p]	MeOH	$C_{11}H_{13}ClN_2O_2$						
3′-Chloro-4-morpholinecarboxanilide	73	129–131		C_6H_6	$C_{11}H_{13}ClN_2O_2$	54.89	54.96	5.45	5.35	11.64	11.72
											11.76
3′,4′-Dichloro-4-morpholinecarboxanilide	23	150–152	157.1–157.8[q]	MeOH–H_2O	$C_{11}H_{12}Cl_2N_2O_2$	48.00	48.65	4.35	4.38	10.18	9.61
							Cl: Calcd., 25.82.		Found, 24.58		

TABLE III (*Continued*)

[a] S. S. Sharp, M. C. Swingle, G. L. McCall, M. B. Weed, and L. E. Cowart, *Agr. Chemicals*, **8**, No. 9, 56 (1953). [b] C. W. Todd, U.S. Patent 2,723,193, November 8, 1955. [c] C. W. Todd, U.S. Patent 2,655,446, October 31, 1953. [d] C. W. Todd, U.S. Patent 2,655,445, October 31, 1953. [e] N. E. Searle, U.S. Patent, 2,655,534, October 13, 1953. [f] A. Kaluszyner, R. Mechoulam, and M. Breuer, *Bull. Res. Council Israel*, 7A, 135 (1958). [g] 43% of the starting material was recovered. [h] 54% of the starting material was recovered. [i] A product was not isolated unless the crude mixture was protected from atmospheric oxidation during purification. [j] 55% of the starting material was recovered. [k] N. E. Searle, U.S. Patent 2,756,135, July 24, 1956. [l] D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957). [m] An authentic sample was prepared from di-*n*-butylamine and *p*-chlorophenyl isocyanate and recrystallized from benzene; mixed m.p. 122°. [n] An authentic sample was prepared from diallylamine and *p*-chlorophenylisocyanate and recrystallized from a hexane–isopropyl alcohol mixture; mixed m.p. 73–74°. [o] R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949). [p] R. A. Henry and W. M. Dehn, *ibid.*, **72**, 2280 (1950). [q] D. J. Beaver, P. J. Stoffel, and P. C. Hamm, U.S. Patent 2,913,322, November 17, 1959.

TABLE IV

PROPERTIES AND ANALYSIS OF 1,1′-ARYLENEBIS(3,3-DIALKYLUREAS)

Compound	Yield, %	M.p., °C.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1,1′-*p*-Phenylenebis(3,3-dimethylurea)	91	307 dec.	$C_{12}H_{18}N_4O_2$	57.59	56.87	7.25	7.17	22.39	21.70
1,1′-*p*-Phenylenebis(3,3-di-*n*-propylurea)	89	221–226	$C_{20}H_{34}N_4O_2$	66.26	65.91	9.45	9.72	15.46	16.42
1,1′-*p*-Phenylenebis(3,3-di-*i*-butylurea)	80	248–253	$C_{24}H_{42}N_4O_2$	68.86	68.31	10.11	10.35	13.39	13.76
1,1′-*p*-Phenylenebis(3,3-dibenzylurea)	70	229–231	$C_{36}H_{34}N_4O_2$	77.95	77.36	6.46	6.04	10.56	10.26 10.17
p-Phenylenebis(4-morpholinecarboxamide)	83	319 dec.	$C_{16}H_{22}N_4O_4$	57.47	57.50	6.63	6.62	16.76	17.23
p-Phenylenebis(piperidinecarboxamide)	89	>360 dec.	$C_{18}H_{26}N_4O_2$	65.42	64.75	7.93	7.84	16.96	17.59 17.59
4,4′-Bis(3,3-dimethylureido)-biphenyl	99	>360 dec.	$C_{18}H_{22}N_4O_2$	66.23	65.50	6.80	6.75	17.17	17.27
4,4′-Bis(3,3-dimethylureido)-3,3′-dimethoxybiphenyl	64	243–245	$C_{20}H_{26}N_4O_4$	62.16	62.37	6.78	6.77	14.50	14.63

the yields of the trialkyl ureas were not high. The conversion of primary amine to dialkylurea varied from 35 to 70%. The properties and yields of various trialkyl ureas are reported in Table V.

Experimental

1,1-Dimethyl-3-phenylurea.—A 2-l. Army surplus oxygen bomb with heating and shaking arrangements that have been described earlier[3] was charged with 20.0 g. (0.21 mole) of aniline, 13.8 g. (0.43 mole) of sulfur, 100 ml. of methanol, and 82 ml. of an 8.75 molar (0.73 mole) aqueous dimethylamine solution and pressurized to 100 p.s.i.g. with carbon monoxide. After the mixture was heated for 2 hr. at 100°, the bomb was vented, and the product was washed from the bomb with methanol. The combined product and washings were filtered while hot and evaporated to dryness on a steam bath. Recrystallization of the residue from 400 ml. of water gave 26.1 g. of 1,1-dimethyl-3-phenylurea, m.p. 131–132°. An additional 1.7 g., m.p. 130–133° (total yield, 79%), was obtained when the mother liquor was partially evaporated on a steam bath, filtered to remove sulfur, and cooled.

Optimum Conditions for 1,1-Dimethyl-3-phenylurea.—A 27-run experiment that could be analyzed by statistical methods was designed to clarify the effect of dilution, reaction temperature, and ratio of dimethylamine to aniline. In each run 0.21 mole of aniline, 0.43 mole of sulfur, and carbon monoxide at 110 p.s.i.g. were used. Temperature levels were 95, 105, and 115°; dimethylamine to aniline ratios were 1:1, 2.5:1, and 4:1; methanol levels were 50 80, and 110 ml.

Analysis of the experimental results revealed that temperature changes between 95 and 115° made no great difference in the yield. Dilution of the reactants with methanol had a deleterious effect that was almost linear. Best yields were obtained with the least amount of solvent. The ratio of dimethylamine to aniline was also important, and the data indicated that the optimum ratio was about 2.4:1.

In an estimation of error, the 95% confidence limit of a single run was ±14.9% based on the theoretical yield from 0.21 mole of aniline. Extrapolating the results, the best yield that can be expected at 105° in no solvent using a 2.4:1 dimethylamine to aniline ratio to 69.8% with limits of 52.8 and 86.8%.

1,1-Di-*n*-butyl-3-phenylurea.—When 0.11 mole of aniline, 0.21 mole of sulfur, 78 ml. of methanol, and carbon monoxide at 100 p.s.i.g. were heated at 100° for 2 hr. with various levels of di-*n*-butylamine, the yield increased as the ratio of dibutylamine to aniline was increased.

Dibutylamine, mole	Yield, %
0.11	34
.22	57
.33	75
.44	74

Subsequently it was demonstrated in a series of experiments that yields could also be increased by using aniline in excess, and that under these conditions better yields were obtained in the absence of solvents. Runs in which 0.078 mole of di-*n*-butylamine and carbon monoxide at 100 p.s.i.g. were used gave the following yields after 2 hr. at 100° when different levels of aniline and sulfur concentration and solvent were employed.

Aniline, mole	Sulfur, mole	Methanol, ml.	Yield, %
0.16	0.12	50	67
.16	.23	0	90; 92
.11	.12	0	63
.11	.23	50	55

Table V

Properties and Analyses of Trialkylureas

Compound	Yield, % Crude	Yield, % Center cut	B.p., °C./mm.	$n^{25}D$	d^{25}_4	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1,1,3-Trimethylurea	..	6	232–233/atm.	...	...	$C_4H_{10}N_2O$	B.p. reported 232.5°/764.5 mm.[a]					
3-*n*-Butyl-1,1-dimethylurea	..	5	100–110/0.8	...	...	$C_7H_{16}N_2O$	58.29	58.4	11.19	11.02	19.43	19.40
3-*i*-Butyl-1,1-diethylurea	51	12	135–138/9	1.4565	0.9223	$C_9H_{20}N_2O$	62.75	62.80	11.70	11.75	16.27	16.37
3-(2-Carboxyethyl)-1,1-di-*n*-butylurea	..	36	M.p. 85[b]	...	...	$C_{12}H_{24}N_2O_3$	58.99	58.65	9.90	9.75	11.47	11.17
							Neut. equiv.: Calcd., 244. Found, 248					
N-(5,5-Di-*n*-butylhydantoyl)glycine	..	5	M.p. 128–129[c]	...	...	$C_{13}H_{24}N_3O$	54.34	54.44	8.77	8.74	14.62	14.37
							Neut. equiv.: Calcd., 286. Found, 289					
3-Cyclohexyl-1,1-di-*n*-propylurea	87	..	M.p. 82–84	...	...	$C_{13}H_{26}N_2O$	68.96	69.37	11.58	11.74	12.37	12.05
								69.24		11.52		12.05
1,1-Di-*i*-butyl-3-*n*-hexylurea	38	11	110–120/13	1.4550	0.8806	$C_{15}H_{32}N_2O$	70.25	70.34	12.58	12.21	10.93	11.05
1,1-Dibenzyl-3-*n*-hexylurea	100	15	190–192/12	1.5370	0.9662	$C_{21}H_{28}N_2O$	77.73	77.53	8.70	8.40	8.64	8.51

[a] A. P. N. Franchimont, *Rec. trav. chim.*, **3**, 216 (1884). [b] From benzene. [c] From water.

Preparation of Other 1,1-Dialkyl-3-arylureas.—The method for preparing compounds in Table III followed with minor variations that given for 1,1-dimethyl-3-phenylurea. In general, the ratio of primary aromatic amine:sulfur: secondary aliphatic amine was 1:2:3. However, for the preparation of 1,1-diisobutyl-3-phenylurea, the ratio was 1:1.5:0.5. In some runs additional carbon monoxide was necessary to ensure a molar excess with respect to sulfur. The quantity of methanol varied from none to 80 ml. Ethanol was used as the solvent in the preparation of 3-(*p*-carbethoxyphenyl)-1,1-dimethylurea.

When 0.054 mole of di-*n*-octylamine, 0.16 mole of aniline, 0.11 mole of sulfur, 4 ml. of methanol, and carbon monoxide at 100 p.s.i.g. were heated 2 hr. at 100°, the only product was a 9% yield of diphenylurea, and 47% of the dioctylamine was recovered unchanged.

Under the conditions described above, aniline and di-2-ethylhexylamine did not react, and 90% of the sulfur was recovered unchanged. No hydrogen sulfide could be detected in the off gases from the bomb.

Aniline and dicyclohexylamine gave a product from which a 38% yield of diphenylurea was isolated and no trisubstituted urea was found.

p-Aminobenzonitrile (25.4 g.) and dimethylamine gave 17.0 g. of a solid, m.p. 193–194° (from ethanol), that contained combined sulfur and did not correspond to the desired urea.

Anal. Found: C, 29.06, 29.23; H, 3.32, 3.30; N, 9.97, 10.12.

When 29.6 g. of *p*-nitroaniline and dimethylamine were used, 62% of the *p*-nitroaniline was recovered unchanged and 5 g. of a solid, m.p. *ca.* 300°, was obtained.

Under similar conditions in the presence of dimethylamine, *o*-nitroaniline was converted in a 51% yield to benzimidazolinone, m.p. 303–307° (from methanol).

1,1′-*p*-Phenylenebis(3,3-dimethylurea).—A 2-l. Magnedash autoclave was charged with 21.6 g. (0.2 mole) of *p*-phenylenediamine, 25.6 g. (0.8 mole) of sulfur, 60 g. (1.3 moles) of dimethylamine, 50 ml. of methanol, and carbon monoxide at 450 p.s.i.g. After the mixture was heated at 100° for 2 hr., the contents of the bomb and additional methanol used in washing the bomb were refluxed for 1 hr., and the hot mixture was filtered. A portion of the residue, recrystallized from dimethylformamide, melted with decomposition at 307°. A total yield of 91% was obtained from the 45.0 g. of residue and an additional 4.6 g. of product that was obtained from the mother liquor.

Other Diureas.—The procedure for the preparation of the compounds in Table IV followed the method for 1,1′-*p*-phenylenebis(3,3-dimethylurea). All of the products were recrystallized from dimethylformamide.

When the diamine was 2,6-diaminopyridine, the only product isolated was a 23% yield of 3-[2-(6-amino)pyridyl]-1,1-dimethylurea, m.p. 184–186° (from water).

Anal. Calcd. for $C_8H_{12}N_4O$: C, 53.31; H, 6.71; N, 31.09. Found: C, 53.79; H, 6.70; N, 30.82.

p-Phenylenediamine and dicyclohexylamine gave a product from which no urea could be isolated, but 50% of the dicyclohexylamine was recovered as the hydrochloride.

Anal. Calcd. for $C_{12}H_{24}ClN$: C, 66.18; H, 11.11; N, 6.43. Found: C, 66.47; H, 10.82; N, 5.91, 5.90.

Under similar conditions *o*-phenylenediamine and dimethylamine, in the presence of carbon monoxide and sulfur, gave a quantitative yield of 2-benzimidazolinone.

1,1-Di-*i*-butyl-3-*n*-hexylurea.—A mixture of 51.6 g. (0.4 mole) of di-*i*-butylamine, 20.2 g. (0.2 mole) of *n*-hexylamine, 6.4 g. (0.2 mole) of sulfur, 200 ml. of methanol, and carbon monoxide at 200 p.s.i.g. were heated and stirred 2 hr. at 120° in a 2-l. autoclave. The product was washed from the autoclave with methanol and heated on a steam bath to remove the solvent. Distillation at 13 mm. afforded three fractions: A, boiling 100–110°, 4.8 g.; B, 110–120°, 5.6 g.;

C, 120–135°, 8.9 g. The cooled residue crystallized and was identified as 1,3-di-*n*-hexylurea, m.p. 72–74°. Analyses shown in Table V are for cut B.

Other Trialkylureas.—The properties and analyses for trialkylureas that were similarly prepared are given in Table V. When dicyclohexylamine was treated with *n*-decylamine under similar conditions, only didecylurea, m.p. 94–95°, and cyclohexylamine were recovered from the mixture.

9-Substituted 3,6-Bis(dimethylamino)acridines

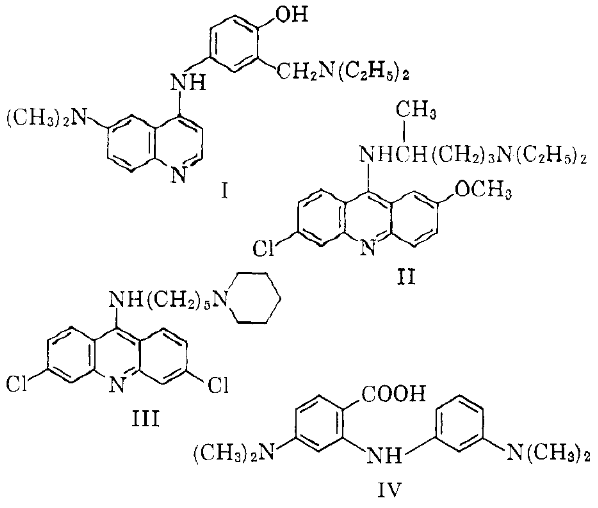
EDWARD F. ELSLAGER

Research Laboratories, Parke, Davis and Co., Ann Arbor, Michigan

Received June 29, 1962

Fusion of 3,6-bis(dimethylamino)acridine and sulfur at 200–210° gave 3,6-bis(dimethylamino)-9(10H)-acridinethione. Alkylation of the sodium salt with the appropriate alkyl halide gave the corresponding 3,6-bis(dimethylamino)-9-(alkylmercapto)acridines. Condensation of 3,6-bis(dimethylamino)-9-(methylmercapto)acridine with various dialkylaminoalkylamines yielded the corresponding 3,6-bis(dimethylamino)-9-(dialkylaminoalkylamino)acridines.

During the coöperative wartime antimalarial program it was observed that α-diethylamino-4-(6-dimethylamino-4-quinolylamino)-*o*-cresol (I) was more active than quinacrine (II) against blood-induced *Plasmodium gallinaceum* in the chick.[1] Further, certain 3,6-disubstituted 9-aminoacridines exhibit unexpectedly high antiparasitic activity. Thus, 3,6-dichloro-9-[5-(1-piperidino)amylamino]-acridine (III) has been reported to be four to eight times as effective as quinacrine against the tapeworm *Hymenolepis nana*.[2] It was therefore of interest to prepare certain 3,6-bis(dimethylamino)-9-aminoacridines (IX) for antiparasitic evaluation.



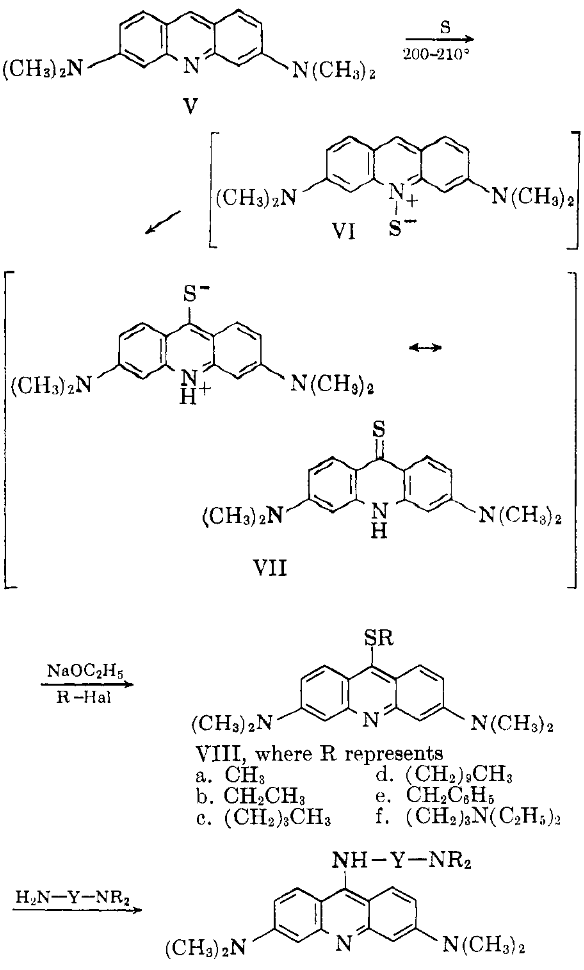
I

II

III

IV

Rather than attempt the preparation of the desired 3,6-bis(dimethylamino)acridines by known methods[2] *via* the difficultly accessible 2-(*m*-dimethylaminoanilino)-4-dimethylaminobenzoic acid (IV), an alternative route was sought. 3,6-Bis(dimethylamino)acridine (V), a commercially available dye known as Acridine Orange,[3] appeared to be an unusually attractive starting material, especially in view of a report by Edinger and Arnold[4] that 9-(10H)-acridinethione is obtained in 85% yield by heating acridine with sulfur in a sealed tube at 190° for four hours. Utilizing a modification of this procedure, equimolar quantities of



VIII, where R represents

a. CH_3	d. $(CH_2)_9CH_3$
b. CH_2CH_3	e. $CH_2C_6H_5$
c. $(CH_2)_3CH_3$	f. $(CH_2)_3N(C_2H_5)_2$

IX, where —Y—NR_2 represents
a. $CHCH_3(CH_2)_3N(C_2H_5)_2$
b. $(CH_2)_3N[(CH_2)_2]_2O$
c. $(CH_2)_3N(CH_2CH_2OH)_2$

---

[1] F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. T. Edwards, Ann Arbor, Mich., 1946, p. 1255.

[2] F. H. Tendick, P. E. Thompson, and E. F. Elslager, U. S. Patent 3,012,036 (1961).

[3] Purchased from National Aniline Division, Allied Chemical Corp., New York 6, N. Y.

[4] A. Edinger and W. Arnold, *J. prakt. Chem.*, **64**, 182 (1901).