Conversion of Biguanides into Substituted *s*-Triazines Assayable by GC or Mass Fragmentography

DAVID ALKALAY ˣ, JOSEPH VOLK, and M. FRED BARTLETT

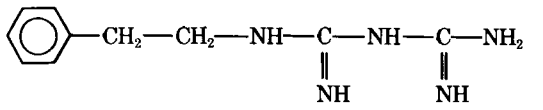
Abstract □ Substituted *s*-triazines were prepared by the treatment of biguanides with various organic acid anhydrides. This reaction permits the ready conversion of the hypoglycemic drugs phenformin, buformin, and metformin and of other analogous biguanides into compounds suitable for GC and mass fragmentographic determination with a high degree of sensitivity. Mass spectral data and Kováts retention indexes are presented for all *s*-triazines prepared for this study.

Keyphrases □ Biguanides—conversion into substituted *s*-triazines, GC and mass fragmentographic analysis □ *s*-Triazines, substituted—synthesized from biguanides, GC and mass fragmentographic analysis □ GC—analysis, *s*-triazines synthesized from biguanides □ Mass fragmentography—analysis, *s*-triazines synthesized from biguanides □ Hypoglycemic agents, oral—GC and mass fragmentographic analysis, *s*-triazines

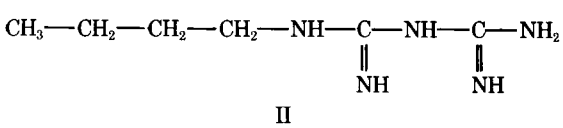
Oral hypoglycemic agents are being used with 20–40% of diabetic patients (1). The two major groups of such drugs are the arylsulfonylureas and the biguanides. The latter include phenformin (I), buformin (II), and metformin (III), which are being widely used in the United States, Germany, and France, respectively (2).

Breidahl *et al.* (3) summarized current views on the yet uncertain mechanism of action of these compounds. Elucidation of this mechanism is hampered by the lack of suitable methodology for assaying biguanides in biological fluids. Published analytical procedures based on fluorescence, colorimetry, or UV absorption lack the necessary specificity and/or sensitivity (4–10). A GC method (11), involving pyrolytic conversion of biguanides into 2,4,6-triamino-1,3,5-triazines, apparently is suitable for assaying buformin in pharmaceutical preparations but not in biological specimens.

The acylation of biguanides has been known to yield *s*-triazines (12–16). The present article describes the use of this reaction for the reproducible conversion of biguanides into substituted *s*-triazines[1] suitable for GC and mass fragmentographic determination.



I



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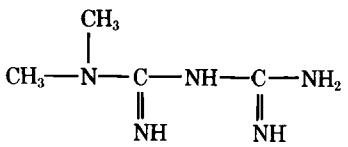


III

EXPERIMENTAL

Chemicals—The following reagents and solvents were used: amformin hydrochloride[2] (IV); buformin hydrochloride[2]; chlorodifluoroacetic anhydride[3]; dichlorofluoroacetic anhydride[4]; methylene chloride[5]; ether[6], anhydrous analytical reagent; 1-ethyl-1-phenethylbiguanide hydrochloride[7] (V), mp 165–166.5°; heptafluorobutyric anhydride[3]; *n*-hexane[5]; 38% hydrochloric acid[8], reagent; magnesium sulfate[8], anhydrous reagent; metformin hydrochloride[9]; 1-(*p*-methoxyphenethyl)biguanide hydrochloride[7] (VI), mp 171–172°; *d*-1-(α-methylphenethyl)biguanide nitrate[7] (VII), mp 141–142.5°, $[\alpha]_D^{25}$ +44.6° (2.16 g of VII in 100 ml of methanol); 1-(*p*-methylphenethyl)biguanide nitrate[7] (VIII), mp 159–160°; pentafluoropropionic anhydride[3]; phenformin hydrochloride[10]; phosphorus pentoxide[8], reagent; potassium hydroxide[8], reagent; sodium hydroxide[8], reagent; triethylamine[11]; and trifluoroacetic anhydride[12].

Preparation of *s*-Triazines—Two acylation methods were employed for the conversion of biguanides into substituted *s*-triazines.

Method A—Aqueous solutions of biguanide salts were made strongly alkaline with 10 *N* KOH and extracted with methylene chloride. Solvent evaporation gave the free bases. To 250-mg amounts of these bases, placed in 40-ml test tubes equipped with screw caps[13], was added 15 ml of a 3% solution of the appropriate organic acid anhydride in methylene chloride. The stoppered test tubes were heated at 50° for 10 min. After cooling, each sample was washed with 3 ml of 2 *N* NaOH. The organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residues were recrystallized from solvent mixtures of ether and *n*-hexane.

Method B—One gram of biguanide salt and 1 ml of triethylamine were placed in a 5-ml acylation tube[14] and cooled to approximately −40°. Four milliliters of the appropriate organic acid anhydride was added to the mixture, and the tube was promptly sealed. Following the exothermic reaction, the tube was heated at 130° for 30 min. After cooling, the reaction mixture was partitioned between 25 ml of cold water and 100 ml of ether. The organic extract was washed consecutively with 1 *N* KOH, 1 *N* HCl, and water. It was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was recrystallized from an ether and *n*-hexane solvent mixture.

Determination of Kováts Retention Indexes—Kováts index-

[1] While completing this investigation, the authors became aware of the independent development of a method for the determination in biological fluids of I–III after conversion into *s*-triazines [S. B. Matin, J. H. Karam, and P. H. Forsham, *Anal. Chem.*, **47**, 545(1975)].

[2] USV Pharmaceutical Corp., Tuckahoe, N.Y.

[3] Pierce Chemical Co., Rockford, Ill.

[4] Alfred Bader Chemicals, Division of Aldrich Chemical Co., Milwaukee, Wis.

[5] Nanograde solvent, Mallinckrodt Chemical Works, St. Louis, Mo.

[6] Mallinckrodt Chemical Works, St. Louis, Mo.

[7] Prepared by A. Wajngurt and M. A. Loo, Ciba-Geigy Corp., Ardsley, N.Y.

[8] J. T. Baker Chemical Co., Phillipsburg, N.J.

[9] Ciba-Geigy Ltd., Basle, Switzerland.

[10] Ciba-Geigy Corp., Summit, N.J.

[11] Eastman Kodak Co., Rochester, N.Y.

[12] Sequanal (grade) chemical, Pierce Chemical Co., Rockford, Ill.

[13] Lined with Teflon (du Pont).

[14] Regis Chemical Co., Morton Grove, Ill.

Table I—List of Substituted *s*-Triazines Derived from Biguanides

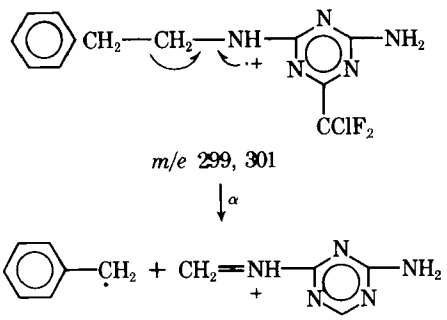
Compound	Name	Method	Yield[a], %
IX	2-Amino-4-phenethylamino-6-trifluoromethyl-*s*-triazine	B	64
X	2-Amino-4-pentafluoroethyl-6-phenethylamino-*s*-triazine	A	71
XI	2-Amino-4-heptafluoropropyl-6-phenethylamino-*s*-triazine	A	72
XII	2-Amino-4-chlorodifluoromethyl-6-phenethylamino-*s*-triazine	A	85
XIII	2-Amino-4-dichlorofluoromethyl-6-phenethylamino-*s*-triazine	A	64
XIV	2-Amino-4-(*p*-methylphenethyl)amino-6-trifluoromethyl-*s*-triazine	A	73
XV	2-Amino-4-(*p*-methylphenethyl)amino-6-pentafluoroethyl-*s*-triazine	A	67
XVI	2-Amino-4-heptafluoropropyl-6-(*p*-methylphenethyl)amino-*s*-triazine	A	60
XVII	2-Amino-4-chlorodifluoromethyl-6-(*p*-methylphenethyl)amino-*s*-triazine	A	73
XVIII	2-Amino-4-(*p*-methoxyphenethyl)amino-6-trifluoromethyl-*s*-triazine	B	68
XIX	2-Amino-4-(α-methylphenethyl)amino-6-trifluoromethyl-*s*-triazine	A	62
XX	2-Amino-4-(α-methylphenethyl)amino-6-pentafluoroethyl-*s*-triazine	A	83[b]
XXI	2-Amino-4-heptafluoropropyl-6-(α-methylphenethyl)amino-*s*-triazine	A	60
XXII	2-Amino-4-chlorodifluoromethyl-6-(α-methylphenethyl)amino-*s*-triazine	A	57
XXIII	2-Amino-4-(*N*-ethyl-*N*-phenethyl)amino-6-trifluoromethyl-*s*-triazine	B	23[b]
XXIV	2-Amino-4-(*N*-ethyl-*N*-phenethyl)amino-6-pentafluoroethyl-*s*-triazine	A	65[b]
XXV	2-Amino-4-(*N*-ethyl-*N*-phenethyl)amino-6-heptafluoropropyl-*s*-triazine	A	51
XXVI	2-Amino-4-chlorodifluoromethyl-6-(*N*-ethyl-*N*-phenethyl)amino-*s*-triazine	A	73
XXVII	2-Amino-4-butylamino-6-trifluoromethyl-*s*-triazine	B	61
XXVIII	2-Amino-4-butylamino-6-pentafluoroethyl-*s*-triazine	A	79
XXIX	2-Amino-4-butylamino-6-heptafluoropropyl-*s*-triazine	A	63
XXX	2-Amino-4-butylamino-6-chlorodifluoromethyl-*s*-triazine	A	90
XXXI	2-Amino-4-pentylamino-6-trifluoromethyl-*s*-triazine	B	77[b]
XXXII	2-Amino-4-pentafluoroethyl-6-pentylamino-*s*-triazine	A	80
XXXIII	2-Amino-4-heptafluoropropyl-6-pentylamino-*s*-triazine	A	54
XXXIV	2-Amino-4-chlorodifluoromethyl-6-pentylamino-*s*-triazine	A	89
XXXV	2-Amino-4-dimethylamino-6-trifluoromethyl-*s*-triazine	B	34

[a] Unless otherwise indicated, the yield is based on material melting within 3° of the analytical sample. [b] Yield based on material melting within 6° of the analytical sample.

es were calculated from the retention times of the investigated compounds and of selected normal saturated hydrocarbons (C_{15}, C_{16}, C_{17}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, and C_{28}). The data were obtained on gas chromatographs equipped with flame-ionization detectors[15,16] and electron-capture (^{63}Ni or Sc^3H foils) detectors[16]. The glass columns [1.8 m (6 ft) × 2 mm i.d.] were filled with nonpolar or moderately polar packings[17]. Argon or nitrogen was used as the carrier gas with a flow rate of approximately 35 ml/min. The injector, detector, and column oven temperatures were maintained at 250, 280, and 210°, respectively.

RESULTS AND DISCUSSION

The substituted *s*-triazines prepared are listed in Table I. They were obtained in good yields by acylation of phenformin, buformin, metformin, and five analogous biguanides (IV–VIII). The latter were selected for use as possible internal standards when assaying the oral hypoglycemic compounds, I–III, in biological fluids. The choice of acylating agents was based on considerations of reactivity, anticipated volatility of the products, and the expectation that the halogenated substituted *s*-triazines will favor high sensitivity in GC detector response and will be suitable for mass fragmentography.



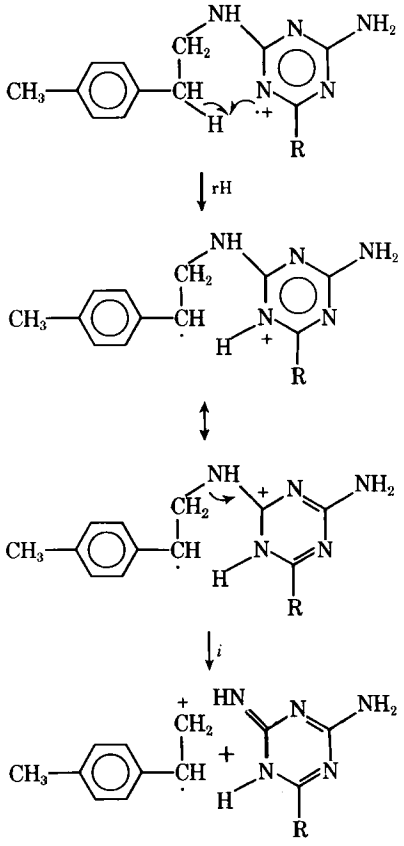
m/e 299, 301

m/e 208, 210

Scheme I

[15] Model 5000 gas chromatograph, Nuclear-Chicago, division of G. D. Searle and Co., Arlington Heights, Ill.
[16] Model 2100 gas chromatograph, Varian, Palo Alto, Calif.
[17] Three percent OV-1 or OV-17 on Chromosorb W HP, 80–100 mesh.

The *s*-triazines, IX–XXXV, are colorless crystalline compounds, whose physical properties are presented in Table II. The proposed structures are supported by elemental analysis results. Additional evidence was derived from the UV and NMR spectral data generated for IX, XVIII, XXVII, XXXI, and XXXV (Table III). The broad UV absorption maxima in the 273–284 and 213–215 nm regions are in agreement with the reported UV absorption of *s*-triazine (17). The NMR data are consistent with the assigned struc-



Scheme II

Table II—Analytical Data for Substituted *s*-Triazines Derived from Biguanides

Compound	Formula	Melting Point[a]	Analysis, %		Optical Rotation[b] $[\alpha]_D^{25}$
			Calc.	Found	
IX	$C_{12}H_{12}F_3N_5$	159.5–160°	C 50.88 H 4.27 N 24.73	50.86 4.56 24.93	—
X	$C_{13}H_{12}F_5N_5$	104–105°	C 46.85 H 3.63 N 21.02	46.87 3.93 21.34	—
XI	$C_{14}H_{12}F_7N_5$	109–110.5°	C 43.87 H 3.16 N 18.27	43.72 3.09 18.34	—
XII	$C_{12}H_{12}ClF_2N_5$	146–147°	C 48.09 H 4.04 N 23.37	47.80 3.99 23.20	—
XIII	$C_{12}H_{12}Cl_2FN_5$	105–106°	C 45.58 H 3.83 N 22.15	45.30 3.81 21.91	—
XIV	$C_{13}H_{14}F_3N_5$	185–186°	C 52.52 H 4.75 N 23.56	52.10 4.83 23.49	—
XV	$C_{14}H_{14}F_5N_5$	112–113°	C 48.41 H 4.06 N 20.17	48.18 3.96 20.21	—
XVI	$C_{15}H_{14}F_7N_5$	146.5–147.5°	C 45.32 H 3.55 N 17.63	45.23 3.82 17.69	—
XVII	$C_{13}H_{14}ClF_2N_5$	162–163°	C 49.76 H 4.50 N 22.32	49.69 4.90 22.35	—
XVIII	$C_{13}H_{14}F_3N_5O$	163.5–164.5°	C 49.84 H 4.50 N 22.36	50.23 4.58 22.21	—
XIX	$C_{13}H_{14}F_3N_5$	106–108°	C 52.52 H 4.75 N 23.56	52.28 4.79 23.37	+16.5° (c = 1.91)
XX	$C_{14}H_{14}F_5N_5$	78–79°	C 48.41 H 4.06 N 20.17	48.07 4.01 20.03	+25.0° (c = 1.23)
XXI	$C_{15}H_{14}F_7N_5$	56–57°	C 45.34 H 3.55 N 17.63	45.44 3.68 17.48	+20.1° (c = 1.98)
XXII	$C_{13}H_{14}ClF_2N_5$[c]	116–117°	C 48.37 H 4.68 N 21.70	48.26 4.45 21.59	+15.6° (c = 1.88)
XXIII	$C_{14}H_{16}F_3N_5$	107–108°	C 54.01 H 5.18 N 22.50	54.28 5.57 22.71	—
XXIV	$C_{15}H_{16}F_5N_5$	95–96°	C 49.86 H 4.46 N 19.38	50.15 4.60 19.36	—
XXV	$C_{16}H_{16}F_7N_5$	97.5–98.5°	C 46.72 H 3.92 N 17.03	46.80 3.89 17.07	—
XXVI	$C_{14}H_{16}ClF_2N_5$	97–98°	C 51.30 H 4.92 N 21.37	51.34 4.76 21.39	—
XXVII	$C_8H_{12}F_3N_5$	89–90°	C 40.85 H 5.14 N 29.78	40.78 5.38 29.74	—
XXVIII	$C_9H_{12}F_5N_5$	113–114°	C 37.90 H 4.24 N 24.56	37.92 4.30 24.51	—
XXIX	$C_{10}H_{12}F_7N_5$	88–89°	C 35.83 H 3.61 N 20.89	35.64 3.65 20.74	—
XXX	$C_8H_{12}ClF_2N_5$	103–104°	C 38.18 H 4.81 N 27.83	37.98 4.93 27.59	—
XXXI	$C_9H_{14}F_3N_5$	104–105°	C 43.37 H 5.66 N 28.10	43.04 5.85 27.99	—
XXXII	$C_{10}H_{14}F_5N_5$	116–117°	C 40.13 H 4.72 N 23.41	40.00 4.65 23.16	—
XXXIII	$C_{11}H_{14}F_7N_5$[d]	76–77.5°	C 35.97 H 4.39 N 19.07	36.03 4.22 18.86	—
XXXIV	$C_9H_{14}ClF_2N_5$	94–94.5°	C 40.68 H 5.31 N 26.36	40.70 5.44 26.19	—
XXXV	$C_6H_8F_3N_5$	153°	C 34.78 H 3.89 N 33.81	35.09 3.98 33.55	—

[a] Determined on a Thomas-Hoover capillary melting-point apparatus and reported uncorrected. [b] Optical rotation measurements were taken at 25° for the D (sodium) line, and "c" refers to milligrams of substance in 100 ml of methanolic solution. [c] Analyzed as the half-hydrate. [d] Analyzed as the monohydrate.

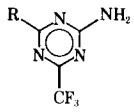
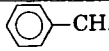
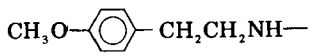


Table III—NMR and UV Spectra of Substituted *s*-Triazines Derived from Biguanides

Compound	R	NMR Spectra[a] δ, ppm	Assignment	Signal	Protons	UV Spectra[b] λ_{max}, nm (ε)
IX		2.85	Ar—CH_2	t	2	273 (4041)
		3.67	N—CH_2	q	2	213 (35,609)
		5.50	C—NH, C—NH_2	br	3	—
		7.20	Ar—H	s	5	—
XVIII		2.80	Ar—CH_2	t	2	284 (4698)
		3.65	N—CH_2	m	2	277 (5635)
		3.77	O—CH_3	s	3	215 (35,736)
		5.40	C—NH, C—NH_2	br	3	—
		6.80	Ar—H_m	d	2	—
		7.08	Ar—H_o	d	2	—
XXVII	$CH_3(CH_2)_3NH$—	0.90	C—CH_3	t	3	273 (3717)
		1.50	C—CH_2	m	4	213 (33,751)
		3.40	N—CH_2	q	2	—
		5.40	C—NH, C—NH_2	br	3	—
XXXI	$CH_3(CH_2)_4NH$—	0.90	C—CH_3	t	3	273 (3742)
		1.50	C—CH_2	m	6	213 (32,850)
		3.40	N—CH_2	q	2	—
		5.60	C—NH, C—NH_2	br	3	—
XXXV	$(CH_3)_2N$—	3.08	N—CH_3	s	6	278 (3430)
		7.40	C—NH_2	br	2	213 (27,433)

[a] Taken on a Varian XL-100 spectrometer with deuterated dimethyl sulfoxide solution of XXXV and deuterochloroform solutions of the remaining compounds, with tetramethylsilane as the internal reference. Singlet, broad singlet, doublet, triplet, quartet, and multiplet splittings are abbreviated s, br, d, t, q, and m, respectively. The H_m and H_o refer to protons in the *meta*- and *ortho*-positions of the *p*-methoxyphenethyl group of XVIII. [b] Determined in methanol with a Cary 14 instrument.

tures. Structural confirmation is provided also by the mass spectral data summarized in Table IV. They show the expected molecular ions and readily recognizable most abundant ion species (base peaks) for all synthetic *s*-triazines.

In the case of triazine XXXV, derived from metformin, the base peak is the molecular ion.

For IX–XIII and XIX–XXXIV, which constitute a majority of the investigated *s*-triazines, the base peak results from alpha cleavage of the molecular ion, as exemplified in Scheme I for the phenformin-derived triazine, XII. The monochloro-substituted triazines, XII, XXII, XXVI, XXX, and XXXIV, yield ^{35}Cl-substituted most abundant ions of the corresponding ^{37}Cl-substituted even electronic species in the expected 3:1 ratio of ^{35}Cl:^{37}Cl. The driving force for the cleavage is probably the electron-donating ability of the alkyl-substituted nitrogen atom.

The base peaks for XIV–XVIII appear to derive from a McLafferty rearrangement of the molecular ion followed by inductive cleavage with charge migration (Scheme II). Even among these *s*-

Table IV—GC and Mass Spectral Data for Substituted *s*-Triazines Derived from Biguanides

Compound	Kováts Indexes 3% OV-1	3% OV-17	Molecular Ion[a]	Most Abundant Ions[a] *m/e* > 60					
IX	2008	2430	283 (30)[b]	192 (100)	91 (43)	104 (38)	193 (20)		
X	1989	2360	333 (27)	242 (100)	91 (35)	104 (27)	243 (9)		
XI	2007	2339	383 (32)	292 (100)	91 (41)	104 (27)	293 (10)		
XII	2209	2667	299 (31)	208 (100)	91 (40)	210 (33)	104 (28)		
XIII	2359	2881	315 (32)	224 (100)	226 (65)	91 (34)	104 (34)	317 (21)	
XIV	2118	2518	297 (40)	118 (100)	192 (70)	105 (29)	180 (19)	117 (18)	119 (11)
XV	2097	2448	347 (33)	118 (100)	242 (71)	105 (31)	230 (18)	119 (16)	117 (9)
XVI	2112	2425	397 (27)	118 (100)	292 (47)	105 (30)	117 (18)	119 (15)	280 (14)
XVII	2295	2741	313 (20)	118 (100)	208 (49)	105 (34)	117 (22)	196 (17)	210 (16)
XVIII	2243	2715	313 (7)	134 (100)	121 (50)	192 (11)	135 (10)		
XIX	1988	2386	297 (3)	206 (100)	91 (24)	207 (10)	138 (8)		
XX	1972	2312	347 (5)	256 (100)	69 (13)	257 (11)	91 (10)		
XXI	1995	2318	397 (7)	306 (100)	69 (18)	91 (13)	307 (12)		
XXII	2171	2601	313 (2)	222 (100)	224 (31)	91 (17)	223 (9)		
XXIII	2014	2365	311 (25)	220 (100)	192 (50)	221 (16)	91 (11)		
XXIV	2025	2305	361 (16)	270 (100)	242 (40)	271 (13)	91 (8)		
XXV	2037	2276	411 (17)	320 (100)	292 (31)	91 (17)	321 (13)		
XXVI	2212	2583	327 (14)	236 (100)	238 (34)	208 (23)	91 (18)	237 (10)	
XXVII	1590	1871	235 (32)	192 (100)	193 (41)	206 (21)	179 (21)	138 (9)	
XXVIII	1575	1824	285 (30)	242 (100)	243 (52)	256 (40)	229 (22)	188 (11)	
XXIX	1590	1803	335 (33)	292 (100)	293 (46)	306 (32)	279 (18)	316 (11)	
XXX	1757	2047	251 (26)	208 (100)	209 (55)	210 (36)	222 (32)	195 (28)	216 (18)
XXXI	1672	1960	249 (31)	192 (100)	193 (43)	206 (22)	179 (18)	220 (14)	138 (9)
XXXII	1672	1915	299 (34)	242 (100)	243 (50)	256 (30)	270 (19)	229 (17)	280 (10)
XXXIII	1686	1894	349 (35)	292 (100)	293 (56)	306 (38)	320 (21)	279 (19)	330 (11)
XXXIV	1850	2150	265 (27)	208 (100)	209 (60)	210 (35)	222 (32)	195 (23)	236 (21)
XXXV	1378	1628	207 (100)	192 (73)	178 (20)	188 (13)			

[a] The mass spectral data were obtained on an AEI model MS 902 magnetic instrument at 70 ev. [b] The relative intensity of each ion is shown in parenthesis as percent of base peak value.

triazines, however, alpha cleavage in accordance with Scheme I is not insignificant. Thus, XIV–XVII, whose methyl substituent may be expected to have only a mild inductive effect, yield ions derived from alpha cleavage, with an abundance second only to that of the base peak.

The GC behavior of the *s*-triazines is good. They elute at moderate temperatures and give essentially symmetrical peaks. The Kováts retention indexes (Table IV) were obtained by computation of the appropriate logarithmic data (18). Independent determinations were also made by use of the Hupe (19) diagram. On the average, results by both methods differed by less than 0.05%.

The conversion of biguanides into substituted *s*-triazines was used for the development of GC and mass fragmentographic methods for assaying phenformin in biological fluids. This treatment permitted the determination of plasma and saliva drug concentration–time profiles and of urinary drug excretion rates following a 100-mg oral dose of phenformin to human volunteers (20). A similar assaying approach is applicable for buformin and metformin. A detailed description of the analytical methodology and its limitations will follow in a separate publication.

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Correlation between Dissolution Characteristics and Absorption of Methaqualone from Solid Dosage Forms

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Abstract □ A methaqualone tablet in two strengths, 150 and 300 mg, was developed. The dissolution rate of an experimental formulation in pH 7.0 phosphate buffer, measured by the resin flask method, was shown to correlate with bioavailability in humans. The dissolution rate criterion was used to develop the final tablet formulation. Bioavailability of this formulation in two strengths was compared with a commercial capsule formulation and a slowly dissolving tablet formulation. Correlation between dissolution rate and bioavailability was shown in freshly prepared methaqualone tablet formulations. Bioavailability of tablets under accelerated stability testing conditions remained unaltered, whereas the dissolution rates in pH 7 phosphate buffer decreased, using the resin flask method. A rotating-flask method was developed, and dissolution in 0.1 *N* HCl at 2 rpm correlated with the bioavailability of both new and aged tablet formulations.

Keyphrases □ Methaqualone—solid dosage forms, dissolution rate correlated with bioavailability □ Dosage forms, solid—dissolution of methaqualone tablets correlated with bioavailability □ Dissolution—methaqualone tablets, correlated with bioavailability □ Bioavailability—methaqualone, correlated with dissolution of tablets

Methaqualone [2-methyl-3-(2-methylphenyl)-4-(3*H*)-quinazolinone] is a sedative–hypnotic and anticonvulsant compound of the 4-quinazolinone series (1). It is usually administered in tablet or capsule form, containing 150–300 mg of the base or hydrochloride salt. The pKa of the conjugate acid is 2.54, and its solubility is 0.3 mg/ml in water (2).

Peak serum levels have been observed within 2 hr after oral administration of methaqualone tablets (3). Other reports (4–6) also indicated the rapid absorption of methaqualone administered in various capsule and tablet formulations. Similar peak levels of methaqualone, within 2 hr, were reported for methaqualone–diphenhydramine hydrochloride tablets and capsules (7). Plasma and urinary excretion data were typical of a dissolution rate-limited process using 2-^{14}C-methaqualone capsules or tablets (4).

The effects of formulation variables on the dissolution of methaqualone were studied (8) in 0.1 *N* HCl, using Levy's beaker method (9); it was concluded