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PICTET-SPENGLER REACTION IN THE SYNTHESIS OF CONDENSED BENZODIAZEPINES. 2.* SYNTHESIS OF NEW DERIVATIVES OF 11,12-DIHYDROQUINAZOLINE-[3,2-*c*][2,3]BENZODIAZEPIN-14(6H)-ONES

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New derivatives of dihydroquinazoline[3,2-c][2,3]benzodiazepin-14(6H)-ones were synthesized using the Pictet-Spengler reaction of 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one with aliphatic and heterocyclic aldehydes in acid media.

Keywords: 3-amino-2-(1,4-benzodioxan-6-ylmethyl)quinazolin-4(3H)-one, 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one, condensed diazepines, dihydroquinazoline[3,2-*c*][2,3]benzodiazepin-14(6H)-ones, Pictet-Spengler cyclization.

The Pictet-Spengler reaction is commonly used in the synthesis of tetrahydroisoquinolines and their heteroanalogs, namely, tetrahydro-β- and tetrahydro-γ-carbolines, tetrahydrobenzofuro[2,3-*c*]- and tetrahydrobenzothieno[2,3-*c*]pyridines [2-4] as well as many isoquinoline and β-carboline alkaloids [5-7]. This reaction is presently employed in numerous variations [8-10].

We should note that the Pictet-Spengler reaction is used mainly for the fusion of a pyridine ring and was not employed for preparing 1,2-benzodiazepine derivatives.

In our previous publication [1], we proposed a new approach for the synthesis of polycondensed diazepines based on formation of the 1,2-diazepine ring in the reaction of 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one (**1a**) and 3-amino-2-(1,4-benzodioxan-6-ylmethyl)quinazolin-4(3H)-one (**1b**) with aromatic aldehydes and paraformaldehyde under conditions of the Pictet-Spengler reaction.

In the present work, we studied the limits of application of this reaction using a broad range of aliphatic, heterocyclic, and functionalized carbonyl compounds. Hydrochloric acid (Method A) and trifluoroacetic acid (Method B) were used as the cyclizing agents.

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* For Communication 1, see [1].

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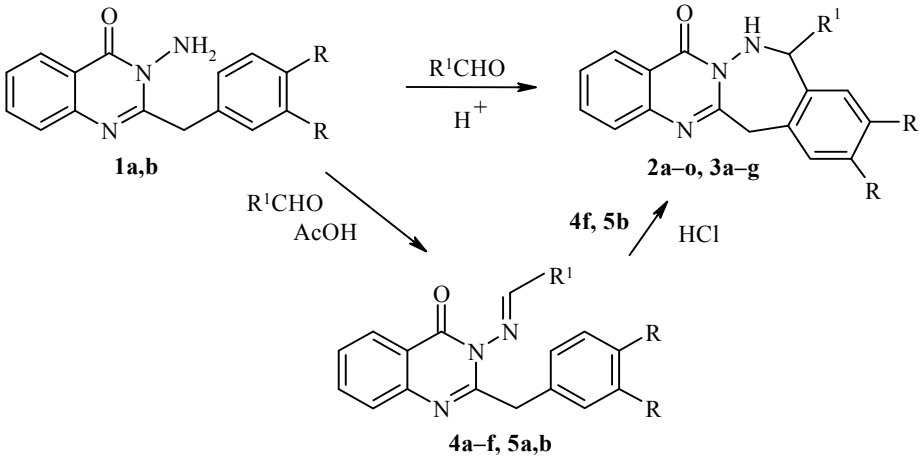
The reaction of 3-aminoquinazolinones **1a** and **1b** with aliphatic aldehydes (acetaldehyde, propionaldehyde, butyraldehyde, and phenylacetaldehyde) in hydrochloric acid proceeds over 10-30 min. Diazepines **2a-c** and **2f** are formed in yields up to 80%. These compounds were taken in stoichiometric amounts due to the possibility of aldol condensations of the indicated aldehydes in acid media. The reaction of amine **1a** with 2-chloro-1,1-dimethoxyethane and 2-bromo-1,1-dibutoxyethane in hydrochloric acid leads to 11-chloromethyldiazepine **2d** and 11-bromomethyldiazepine **2e** in yields not less than 90%. Carrying out the reaction in trifluoroacetic acid in the case of aliphatic aldehydes is not feasible due to low yields and formation of polymeric products.



1 a R = OMe, **b** R = OCH_2CH_2O; **2 a-o** R = OMe, **a** R^1 = Me, **b** R^1 = Et, **c** R^1 = Pr, **d** R^1 = $ClCH_2$, **e** R^1 = CH_2Br, **f** R^1 = CH_2Ph, **g** R^1 = COPh, **h** R^1 = benzofur-2-yl, **i** R^1 = benzofur-3-yl, **j** R^1 = 5-nitrofur-2-yl, **k** R^1 = 4-bromothien-2-yl, **l** R^1 = 5-chlorothien-2-yl, **m** R^1 = pyrid-3-yl, **n**) R^1 = quinol-2-yl, **o** R^1 = quinol-4-yl; **3 a-g** R = OCH_2CH_2O, **a** R^1 = Et, **b** R^1 = $ClCH_2$, **c** R^1 = benzofur-2-yl, **d** R^1 = benzofur-3-yl, **e** R^1 = 4-bromothien-2-yl, **f** R^1 = pyrid-4-yl, **g** R^1 = quinol-4-yl; **4 a-g** R = OMe, **a** R^1 = indol-3-yl, **b** R^1 = 1-methylindol-3-yl, **c** R^1 = 1-benzylindol-3-yl, **d** R^1 = 1,2-dimethylindol-3-yl, **e** R^1 = thien-2-yl, **f** R^1 = 5-propylthien-2-yl, **g** 5-methylfur-2-yl; **5 a,b** R = OCH_2CH_2O, **a** R^1 = 5-chlorothien-2-yl, **b** R^1 = 4-bromothien-2-yl

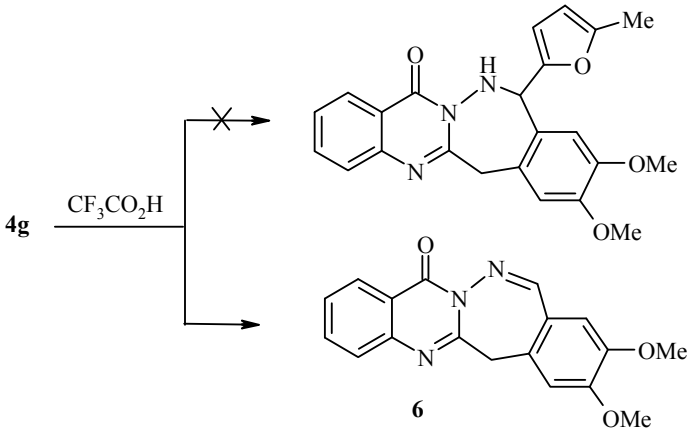
Heterocyclic indole aldehydes, namely, indole-3-carboxaldehyde, 2-methylindole-3-carboxaldehyde, 1-methylindole-3-carboxaldehyde, 1-benzylindole-3-carboxaldehyde, and 1,2-dimethylindole-3-carboxaldehyde as well as furfural and thiophene-2-carboxaldehyde do not form the corresponding diazepines either by Method A or Method B. Thus, heating a mixture of amine **1a** and indole aldehydes in trifluoroacetic acid at reflux for 4-5 h yields aldimines **4a-d**. Only tar formation from the aldehydes is observed in hydrochloric acid and only starting amine **1a** could be isolated from the reaction mixture. Heating aldimines **4a-c** in hydrochloric and trifluoroacetic acids at reflux for 8-10 h leads to polymeric products, which is attributed to the instability of the incompletely substituted pyrrole ring in acid media, while aldimine **4d** is retrieved unchanged even after heating in hydrochloric and trifluoroacetic acids at reflux for 24 h, which is attributed to the low activity of this aldimine due to the electron-donor effect of the pyrrole ring.

Furfural and thiophene-2-carboxaldehyde are also unstable in strongly acidic media [11, 12] and do not form diazepines either by Method A or Method B. Attempts to cyclize aldimine **4e** in trifluoroacetic acid and in hydrochloric acid also were unsuccessful. More stable 5-propylthiophene-2-carboxaldehyde reacts with amine **1a** in hydrochloric acid to give diazepine in about 10% yield (indicated by the integral signal intensities

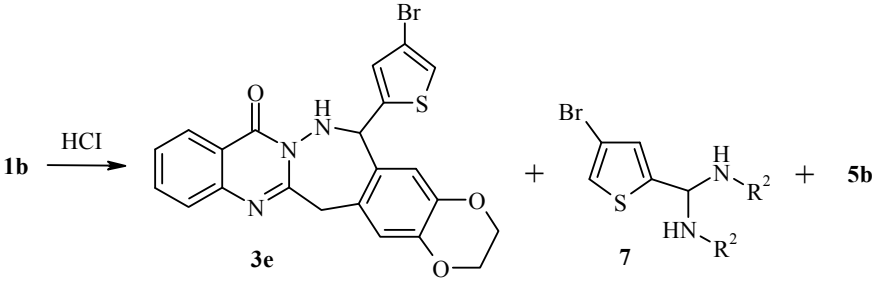
in the ^{1}H NMR spectra), which could not be isolated as a pure compound. The formation of diazepines is readily detected relative to the characteristic doublets for the H-6 protons in the ^{1}H NMR spectra with J = 11-12 Hz and singlets for aromatic protons H-7 and H-10.

In contrast to indole-3-carboxaldehyde, isosteric benzo[*b*]furan-2-carboxaldehyde and benzo[*b*]furan-3-carboxaldehyde react smoothly to give diazepines **2h**,**i**, **3c**,**d**. A nitro group in the furan ring in the case of 5-nitrofurfural enhances stability of the furan ring, while halogen atoms stabilize the thiophene ring in 5-chlorothiophene-2-carboxaldehyde and 4-bromothiophene-2-carboxaldehyde, which permits preparation of the corresponding diazepines **2j-l**.

An unexpected result was obtained for the reaction of 5-methylfurfural with amine **1a**. Heating previously prepared Schiff's base **4g** in trifluoroacetic acid gave quinazoline[3,2-*c*][2,3]benzodiazepin-14(6H)-one **6**, which is in accord with our previous results [9]. The protons of the 6-CH_2 group in the ^{1}H NMR spectrum of diazepine **6** appear as a singlet at 3.95 ppm.



We experimentally demonstrated that the susceptibility toward electrophilic substitution of the 1,4-benzodioxane fragment in aminoquinazolinone **1b** is lower than for the 3,4-dimethoxyphenyl fragment. Thus, diazepine **3e** (30%), azomethine **5b** (50%), and aminal **7** (20%) were isolated upon heating amine **1b** with 4-bromothiophene-2-carboxaldehyde in hydrochloric acid for 4 h and work-up of the reaction mixture (Method A). Heating the mixture at reflux for 10 h produced partial tar formation, while diazepine **3e** is formed in 30% yield. Under the same conditions (heating at for 4 h), aminoquinazolinone **1a** and 4-bromothiophene-2-carboxaldehyde give the corresponding diazepine **2k** in 63% yield.



R^2 = 3-[2-(1,4-benzodioxan-6-ylmethyl)quinazolin-4(3H)-one]

5-Chlorothiophene-2-carboxaldehyde is even less active and reacts with aminoquinazolinone **1b** in hydrochloric acid to give only azomethine **5a**. The corresponding diazepine was identified in the ^{1}H NMR spectrum of the reaction mixture in only trace amounts.

TABLE 1. Characteristics of Synthesized Compounds **2-11**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	$t_{reac.}$, h	Yield, %*
		C	H	Hal	N	S			
1	2	3	4	5	6	7	8	9	10
2a	$C_{19}H_{19}N_3O_3$	67.91 / 67.64	5.35 / 5.68		12.37 / 12.45		177	1	70
2b	$C_{20}H_{21}N_3O_3$	68.64 / 68.36	5.91 / 6.02		12.01 / 11.96		139	1	80
2c	$C_{21}H_{23}N_3O_3$	68.93 / 69.02	6.51 / 6.34		11.72 / 11.50		127	1	80
2d	$C_{19}H_{18}ClN_3O_3$	61.14 / 61.38	4.73 / 4.88	9.42 / 9.53	11.35 / 11.30		195-196	1	98
2e	$C_{19}H_{18}BrN_3O_3$	54.59 / 54.82	4.52 / 4.36	19.10 / 19.19	10.16 / 10.09		193	1	95
2f	$C_{25}H_{23}N_3O_3$	72.87 / 72.62	5.76 / 5.61		10.37 / 10.16		174	1	65
2g	$C_{25}H_{21}N_3O_4$	70.34 / 70.25	5.13 / 4.95		9.81 / 9.83		282-285 (dec.)	8	*65*
2h	$C_{26}H_{21}N_3O_4$	71.21 / 71.06	4.66 / 4.82		9.60 / 9.56		238-239	3.5	72
2i	$C_{26}H_{21}N_3O_4$	71.16 / 71.06	4.55 / 4.82		9.49 / 9.56		147-148	8	*67*
2j	$C_{22}H_{18}N_4O_6$	60.67 / 60.83	4.00 / 4.18		13.02 / 12.90		dec. > 230	8	*69*
2k	$C_{22}H_{18}BrN_3O_3S$	54.88 / 54.55	3.72 / 3.75	16.57 / 16.50	8.63 / 8.68	6.78 / 6.62	222	8	*63*
2l	$C_{22}H_{18}ClN_3O_3S$	60.34 / 60.07	3.99 / 4.12	8.01 / 8.06	9.59 / 9.55	7.43 / 7.29	201-202	3.5 9	40 *50*
2m	$C_{23}H_{20}N_4O_3$	68.83 / 68.99	5.16 / 5.03		14.10 / 13.99		202-203	8	*46*
2n	$C_{27}H_{22}N_4O_3$	72.11 / 71.99	5.03 / 4.92		12.58 / 12.44		dec. > 188	3.5	50
2o	$C_{27}H_{22}N_4O_3$	72.16 / 71.99	4.98 / 4.92		12.53 / 12.44		256-257 (dec.)	3.5	85
3a	$C_{20}H_{19}N_3O_3$	68.93 / 68.75	5.39 / 5.48		12.17 / 12.03		225	1	94
3b	$C_{19}H_{16}ClN_3O_3$	61.61 / 61.71	4.11 / 4.36	9.67 / 9.59	11.23 / 11.36		233-234	1	72
3c	$C_{26}H_{19}N_3O_4$	71.45 / 71.39	4.12 / 4.38		9.68 / 9.61		233-234	4	69
3d	$C_{26}H_{19}N_3O_4$	71.56 / 71.39	4.49 / 4.38		9.59 / 9.61		253-255	4	70
3e	$C_{22}H_{16}BrN_3O_3S$	54.92 / 54.78	3.21 / 3.34	16.43 / 16.57	8.91 / 8.71	6.75 / 6.65	233-235	10	30

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
3f	$C_{23}H_{18}N_4O_3$	69.51 69.34	4.63 4.55		13.98 14.06		241-242 (dec.)	4	80
3g	$C_{27}H_{20}N_4O_3$	72.37 72.31	4.33 4.49		12.55 12.49		dec. >260	4	80
4a	$C_{26}H_{22}N_4O_3$	71.32 71.22	5.00 5.06		12.74 12.78		234	4	*27*
4b	$C_{27}H_{24}N_4O_3$	71.66 71.67	5.12 5.35		12.41 12.38		175	5	*50*
4c	$C_{33}H_{28}N_4O_3$	75.08 74.98	5.53 5.34		10.68 10.60		206	5	*50*
4d	$C_{28}H_{26}N_4O_3$	72.13 72.09	5.53 5.62		12.11 12.01		200-202	24	*82*
4e	$C_{22}H_{19}N_3O_3S$	64.91 65.17	4.92 4.72		10.39 10.36	7.92 7.91	163		60
4f	$C_{25}H_{25}N_3O_3S$	67.20 67.09	5.58 5.63		9.54 9.39	7.01 7.16	109		64
4g	$C_{23}H_{21}N_3O_4$	68.56 68.47	5.08 5.25		10.40 10.42		103		59
5a	$C_{22}H_{16}ClN_3O_3S$	60.56 60.34	3.84 3.68	8.04 8.10	9.52 9.60	7.44 7.32	134-135	4	60
5b	$C_{22}H_{16}BrN_3O_3S$	54.61 54.78	3.59 3.34	16.42 16.57	8.67 8.71	6.61 6.65	166-167	4	50
6	$C_{18}H_{15}N_3O_3$	68.95 68.86	6.13 6.16		10.78 10.71		233-235 (dec.)	6	*40*
7	$C_{39}H_{31}BrN_6O_6S$	59.24 59.17	4.02 3.95	10.17 10.09	10.54 10.62	4.21 4.05	221-223	4	20
8a	$C_{25}H_{20}N_4O_4$	68.31 68.17	4.66 4.58		12.65 12.72		284	8	*70*
8b	$C_{25}H_{18}N_4O_4$	68.39 68.49	3.99 4.14		12.61 12.78		dec. > 305	4	70
9	$C_{26}H_{19}N_3O_5$	68.82 68.87	4.43 4.22		9.41 9.27		259	1 8	96 *67*
10	$C_{20}H_{19}N_3O_5$	63.04 62.99	4.97 5.02		11.20 11.02		dec. > 160	1	100
11	$C_{25}H_{23}N_3O_3$	72.44 72.62	5.72 5.61		10.27 10.16		212-213	24	*38.8*

* Products **2a-o**, **3a-g**, **4a-d**, **5a**,**b**, **6**, **7**, **8a**,**b,** and **9-11** were obtained by Methods A and B. The yields using Method B are indicated by italics.

TABLE. 2. ^{1}H NMR Spectra of Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2a	1.49 (3H, d, *J* = 6.8, CH_3); 3.70 and 3.78 (6H, s, 8- and 9-OCH_3); 3.87 and 4.79 (2H, br. d, H-6); 4.50 (1H, q, *J* = 6.8, H-11); 6.58 (1H, s, H-7); 6.71 (1H, br. s, NH); 6.74 (1H, s, H-10); 7.41 (1H, t, *J* = 8.0, H-2); 7.54 (1H, d, *J* = 8.0, H-4); 7.69 (1H, t, *J* = 8.0, H-3); 8.11 (1H, d, *J* = 8.0, H-1)
2b	1.04 (3H, t, *J* = 6.8, CH_3); 1.91 and 2.05 (2H, m, *J* = 6.8, C$\underline{H_2}$Me); 3.60 and 5.04 (2H, d, *J* = 13.2, 6-CH_2); 3.70 and 3.79 (6H, s, 8- and 9-OCH_3); 4.40 (1H, m, H-11); 6.54 (1H, br. s, NH); 6.57 (1H, s, H-7); 6.74 (1H, s, H-10); 7.40 (1H, t, *J* = 8.0, H-2); 7.53 (1H, d, *J* = 8.0, H-4); 7.67 (1H, t, *J* = 8.0, H-3); 8.10 (1H, d, *J* = 8.0, H-1)
2c	1.02 (3H, t, *J* = 6.8, CH_3); 1.48 and 1.68 (2H, m, C$\underline{H_2}$$CH_2$Me); 1.92 (2H, m, CH_2C$\underline{H_2}$Me); 3.63 and 5.06 (2H, d, *J* = 13.2, H-6); 3.73 and 3.82 (6H, s, 8- and 9-OCH_3); 4.44 (1H, m, H-11); 6.56 (1H, br. s, NH); 6.57 (1H, s, H-7); 6.77 (1H, s, H-10); 7.43 (1H, t, *J* = 8.0, H-2); 7.56 (1H, d, *J* = 8.0, H-4); 7.71 (1H, t, *J* = 8.0, H-3); 8.13 (1H, d, *J* = 8.0, H-1)
2d	3.74 and 3.83 (6H, s, 8- and 9-OCH_3); 3.68 and 5.07 (2H, d, *J* = 12.8, H-6); 3.85 and 4.31 (2H, d, *J* = 11.6, CH_2Cl); 4.72 (1H, m, H-11); 6.82 (1H, s, H-7); 6.84 (1H, s, H-10); 7.44 (1H, t, *J* = 8.0, H-2); 7.57 (1H, d, *J* = 8.0, H-4); 7.72 (1H, t, *J* = 8.0, H-3); 8.15 (1H, d, *J* = 8.0, H-1)
2e	3.72 and 3.80 (6H, s, 8- and 9-OCH_3); 3.65 and 5.06 (2H, br. d, H-6); 3.76 and 4.22 (2H, d, *J* = 10.8, CH_2Br); 4.70 (1H, m, H-11); 6.83 (1H, s, H-7); 6.85 (1H, s, H-10); 7.44 (1H, t, *J* = 8.0, H-2); 7.57 (1H, d, *J* = 8.0, H-4); 7.72 (1H, t, *J* = 8.0, H-3); 8.11 (1H, d, *J* = 8.0, H-1)
2f	3.13 (1H, dd, *J* = 7.4, *J* = 8.0, CH_2Ph); 3.31 (1H, dd, *J* = 7.4, *J* = 4.4, CH_2Ph); 3.55 and 4.93 (2H, d, *J* = 12.8, H-6); 3.65 and 3.82 (6H, s, 8- and 9-OCH_3); 4.75 (1H, m, H-11); 6.51 (1H, d, *J* = 2.4, NH); 6.60 (1H, s, H-7); 6.75 (1H, s, H-10); 7.25-7.30 (5H, m, C_6H_5); 7.39 (1H, t, *J* = 8.0, H-2); 7.53 (1H, d, *J* = 8.0, H-4); 7.67 (1H, t, *J* = 8.0, H-3); 8.07 (1H, d, *J* = 8.0, H-1)
2g	3.09 (2H, s, H-6); 3.57 and 3.96 (6H, s, 8 and 9-OCH_3); 6.33 (1H, s, H-7); 7.17 (1H, d, *J* = 1.6, H-11); 7.34 (1H, t, *J* = 7.6, H-4'); 7.47 (2H, t, *J* = 7.6, H-3',5'); 7.59 (1H, t, *J* = 8.0, H-2); 7.74 (3H, m, H-4,2',6'); 7.84 (1H, t, *J* = 8.0, H-3); 7.99 (1H, br. s, NH); 8.08 (1H, d, *J* = 8.0, H-1)
2h	3.60 and 3.84 (6H, s, 8- and 9-OCH_3); 4.45 (2H, br. s, H-6); 5.85 (1H, s, H-11); 6.48 (1H, br. s, NH); 6.57 (1H, s, H-7); 6.93 (1H, s, H-10); 7.14 (1H, t, *J* = 8.0, H-5' benzofuran); 7.21 (1H, t, *J* = 8.0, H-6' benzofuran); 7.30 (1H, s, H-3' benzofuran); 7.38 (2H, m, H-2,7' benzofuran); 7.44 (1H, d, *J* = 8.0, H-4' benzofuran); 7.59 (1H, d, *J* = 8.0, H-4); 7.72 (1H, t, *J* = 8.0, H-3); 7.92 (1H, d, *J* = 8.0, H-1)
2i	3.56 and 3.85 (6H, s, 8- and 9-OCH_3); 4.09 and 5.14 (2H, br. d, 6-CH_2); 5.81 (1H, s, H-11); 6.52 (1H, s, H-7); 6.90 (1H, br. s, NH); 6.96 (1H, s, H-10); 7.12 (1H, br. t, H-5' benzofuran); 7.26 (1H, t, *J* = 8.0, H-6' benzofuran); 7.45 (1H, t, *J* = 8.0, H-2); 7.51 (2H, m, H-4',7' benzofuran); 7.62 (1H, d, *J* = 8.0, H-4); 7.76 (1H, t, *J* = 8.0, H-3); 7.95 (1H, br. s, H-2' benzofuran); 8.07 (1H, d, *J* = 8.0, H-1)
2j	3.68 and 3.87 (6H, s, 8- and 9-OCH_3); 4.11 and 4.96 (2H, d, *J* = 12.8, 6-CH_2); 5.92 (1H, d, *J* = 2.4, H-11); 6.19 (1H, br. s, NH); 6.61 (1H, s, H-7); 6.95 (1H, s, H-10); 7.31 (1H, d, *J* = 4.0, H-3' furan); 7.44 (1H, t, *J* = 8.0, H-2); 7.61 (1H, d, *J* = 8.0, H-4); 7.65 (1H, br. d, H-4' furan); 7.76 (1H, t, *J* = 8.0, H-3); 8.00 (1H, d, *J* = 8.0, H-1)
2k	3.61 and 3.81 (6H, s, 8- and 9-OCH_3); 4.18 and 4.69 (2H, d, *J* = 12.4, 6-CH_2); 5.90 (1H, d, *J* = 2.4, H-11); 6.50 (1H, s, H-7); 6.90 (1H, s, H-10); 7.09 (1H, s, H-3'); 7.14 (1H, br. s, NH); 7.35 (1H, s, H-5'); 7.43 (1H, t, *J* = 8.0, H-2); 7.58 (1H, d, *J* = 8.0, H-4); 7.73 (1H, t, *J* = 8.0, H-3); 8.04 (1H, d, *J* = 8.0, H-1)
2l	3.62 and 3.82 (6H, s, 8- and 9-OCH_3); 4.13 and 4.74 (2H, d, *J* = 13.2, 6-CH_2); 5.83 (1H, d, *J* = 2.4, H-11); 6.51 (1H, s, H-7); 6.83 (1H, d, *J* = 4.0, H-4'); 6.89 (1H, s, H-10); 6.96 (1H, d, *J* = 4.0, H-3'); 7.09 (1H, br. s, NH); 7.44 (1H, t, *J* = 8.0, H-2); 7.59 (1H, d, *J* = 8.0, H-4); 7.74 (1H, t, *J* = 8.0, H-3); 8.06 (1H, d, *J* = 8.0, H-1)
2m	3.53 and 3.81 (6H, s, 8- and 9-OCH_3); 4.21 and 4.82 (2H, d, *J* = 12.0, CH_2); 5.64 (1H, d, *J* = 2.0, H-11); 6.31 (1H, s, H-7); 6.94 (1H, s, H-10); 7.07 (1H, br. s, NH); 7.19 (1H, t, *J* = 5.2, H-5'); 7.42 (1H, t, *J* = 8.0, H-3); 7.47 (1H, br. d, H-6'); 7.59 (1H, d, *J* = 8.0, H-4); 7.73 (1H, t, *J* = 8.0, H-2); 7.98 (1H, d, *J* = 8.0, H-1); 8.42 (1H, d, *J* = 5.2, H-4'); 8.51 (1H, s, H-2')

TABLE. 2 (continued)

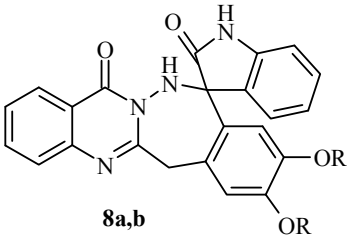
1	2
2n	3.47 and 3.80 (6H, s, 8- and 9-OCH_3); 4.22 and 4.93 (2H, d, *J* = 13.2, CH_2); 5.82 (1H, d, *J* = 2.4, H-11); 6.45 (1H, s, H-7); 7.02 (1H, s, H-10); 7.30 (1H, br. s, NH); 7.33 (1H, d, *J* = 8.0, H-5'); 7.42 (1H, t, *J* = 8.0, H-3); 7.56 (1H, t, *J* = 8.0, H-7'); 7.63 (1H, d, *J* = 8.0, H-4); 7.69 (1H, t, *J* = 8.0, H-6'); 7.76 (1H, t, *J* = 8.0, H-2); 7.85 (1H, d, *J* = 8.0, H-3'); 7.89 (1H, d, *J* = 8.0, H-8'); 7.93 (1H, d, *J* = 8.0, H-1); 8.21 (1H, d, *J* = 8.0, H-4')
2o	3.43 and 3.84 (6H, s, 8- and 9-OCH_3); 4.10 and 5.11 (2H, d, *J* = 13.2, CH_2); 6.26 (1H, s, H-11); 6.35 (1H, br. s, NH); 7.01 (2H, s, H-7,10); 7.07 (1H, br. s, H-7'); 7.45 (1H, t, *J* = 8.0, H-3); 7.62 (1H, d, *J* = 8.0, H-4); 7.71–7.81 (3H, m, H-2,5',6'); 8.04 (1H, d, *J* = 8.0, H-1); 8.08 (1H, d, *J* = 8.0, H-3'); 8.66 (1H, br. d, H-8'); 8.74 (1H, br. d, H-2')
3a	1.02 (3H, t, *J* = 6.8, $CH_2C\underline{H_3}$); 1.89 and 2.05 (2H, m, *J* = 6.8, $C\underline{H_2}Me$); 3.89 and 5.02 (2H, d, *J* = 12.8, 6-CH_2); 4.20 (4H, m, OCH_2CH_2O); 4.38 (1H, br. m, H-11); 5.92 (1H, br. s, NH); 6.57 (1H, s, H-7); 6.76 (1H, s, H-10); 7.53 (1H, t, *J* = 8.0, H-2); 7.74 (1H, d, *J* = 8.0, H-4); 7.82 (1H, t, *J* = 8.0, H-3); 8.15 (1H, d, *J* = 8.0, H-1)
3b	3.83 and 4.96 (2H, d, *J* = 12.8, H-6); 3.89 and 4.19 (2H, m, CH_2Cl); 4.19 (4H, m, OCH_2CH_2O); 4.69 (1H, br. m, H-11); 5.23 (1H, br. s, NH); 6.79 (1H, s, H-7); 6.80 (1H, s, H-10); 7.51 (1H, t, *J* = 8.0, H-2); 7.66 (1H, d, *J* = 8.0, H-4); 7.79 (1H, t, *J* = 8.0, H-3); 8.13 (1H, d, *J* = 8.0, H-1)
3c	4.16 (4H, m, OCH_2CH_2O); 4.41 (2H, br. s, H-6); 5.82 (1H, s, CH); 6.50 (1H, s, H-7); 6.58 (1H, br. s, NH); 6.90 (1H, s, H-10); 7.14 (1H, t, *J* = 8.0, H-5' benzofuran); 7.18 (1H, d, *J* = 8.0, H-4' benzofuran); 7.22 (1H, t, *J* = 8.0, H-6' benzofuran); 7.40 (1H, t, *J* = 8.0, H-2); 7.45 (1H, s, H-3' benzofuran); 7.49 (1H, d, *J* = 8.0, H-7' benzofuran); 7.61 (1H, d, *J* = 8.0, H-4); 7.75 (1H, t, *J* = 8.0, H-3); 7.89 (1H, d, *J* = 8.0, H-1)
3d	3.94 and 5.07 (2H, br. d, 6-CH_2); 4.10 (4H, m, OCH_2CH_2O); 5.67 (1H, s, CH); 6.41 (1H, s, H-7); 6.78 (1H, br. s, NH); 6.81 (1H, s, H-10); 7.06 (1H, br. t, H-5' benzofuran); 7.19 (1H, t, *J* = 8.0, H-6' benzofuran); 7.39 (1H, t, *J* = 8.0, H-2); 7.42 (2H, m, H-4',7' benzofuran); 7.55 (1H, d, *J* = 8.0, H-4); 7.70 (1H, t, *J* = 8.0, H-3); 7.92 (1H, br. s, H-2' benzofuran); 8.02 (1H, d, *J* = 8.0, H-1)
3e	4.05 and 4.73 (2H, br. s, 6-CH_2); 4.17 (4H, m, OCH_2CH_2O); 5.81 (1H, br. s, H-11); 6.45 (1H, s, H-7); 6.78 (1H, s, H-10); 7.09 (1H, s, H-3'); 7.31 (1H, s, H-5'); 7.42 (1H, t, *J* = 8.0, H-2); 7.56 (1H, d, *J* = 8.0, H-4); 7.71 (1H, t, *J* = 8.0, H-3); 8.06 (1H, d, *J* = 8.0, H-1)
3f	4.03 and 4.88 (2H, d, *J* = 13.2, CH_2); 4.15 (4H, m, OCH_2CH_2O); 5.49 (1H, s, H-11); 6.25 (1H, s, H-7); 6.82 (1H, s, H-10); 6.90 (1H, s, NH); 7.25 (2H, d, *J* = 5.6, H-3',5'); 7.40 (1H, t, *J* = 8.0, H-3); 7.57 (1H, d, *J* = 8.0, H-4); 7.70 (1H, d, *J* = 8.0, H-2); 8.04 (1H, d, *J* = 8.0, H-1); 8.46 (2H, d, *J* = 5.6, H-2',6')
3g	3.99 and 5.13 (2H, d, *J* = 13.2, CH_2); 4.13 (4H, m, OCH_2CH_2O); 6.18 (1H, s, H-11); 6.23 (1H, br. s, NH); 6.90 (1H, s, H-7); 6.97 (1H, s, H-10); 7.19 (1H, br. s, H-7'); 7.45 (1H, t, *J* = 8.0, H-3); 7.61 (1H, d, *J* = 8.0, H-4); 7.67–7.79 (3H, m, H-2,5',6'); 8.07 (2H, m, H-1,3'); 8.56 (1H, br. d, H-8'); 8.77 (1H, br. d, H-2')
4a	3.14 and 3.65 (6H, s, 3',4'-OCH_3); 4.22 (2H, s, CH_2); 6.67 (1H, d, *J* = 8.4, H-5' veratrole); 6.69 (1H, s, H-2' veratrole); 6.77 (1H, d, *J* = 8.4, H-6' veratrole); 7.23 (2H, m, H-5',6' indole); 7.49 (2H, m, H-6, H-7' indole); 7.69 (1H, d, *J* = 8.4, H-8); 7.77 (1H, t, *J* = 8.4, H-7); 7.88 (1H, d, *J* = 2.4, H-2' indole); 8.15 (1H, d, *J* = 8.4, H-5); 8.27 (1H, d, *J* = 8.4, H-4' indole); 8.51 (1H, s, CH=N); 11.91 (1H, s, NH indole)
4b	3.25 (3H, s, 1-CH_3); 3.65 and 3.88 (6H, s, 3'- and 4'-OCH_3); 4.22 (2H, s, CH_2); 6.76 (3H, s, H-2',5',6' veratrole); 7.30 (2H, m, H-5',6' indole); 7.57 (2H, m, H-6,7' indole); 7.79 (2H, m, H-7,8); 7.96 (1H, s, H-2' indole); 8.19 (2H, m, H-5,4' indole); 8.60 (1H, s, CH=N)
4c	3.20 and 3.68 (6H, s, 3'- and 4'-OCH_3); 4.24 (2H, s, CH_2); 5.49 (2H, s, CH_2 benzyl); 6.65 (1H, d, *J* = 8.4, H-5' veratrole); 6.72 (1H, s, H-2' veratrole); 6.78 (1H, d, *J* = 8.4, H-6' veratrole); 7.26 (5H, m, H benzyl); 7.33 (2H, m, H-5',6' indole); 7.45 (2H, m, H-6,7' indole); 7.69 (1H, d, *J* = 8.0, H-8); 7.74 (1H, t, *J* = 8.0, H-7); 7.96 (1H, s, H-2' indole); 8.17 (1H, d, *J* = 8.0, H-5); 8.32 (1H, d, *J* = 8.0, H-4' indole); 8.53 (1H, s, CH=N)
4d	2.45 (3H, s, 2-CH_3); 3.20 (3H, s, 1-CH_3); 3.70 and 3.80 (6H, s, 3'- and 4'-OCH_3); 4.21 (2H, s, CH_2); 6.65 (1H, s, H-2' veratrole); 6.67 (1H, d, *J* = 8.0, H-5' veratrole); 6.76 (1H, d, *J* = 8.0, H-6' veratrole); 7.24 (2H, m, H-5',6' indole); 7.47 (2H, m, H-6,7' indole); 7.70 (1H, d, *J* = 8.0, H-8); 7.77 (1H, t, *J* = 8.0, H-7); 8.16 (1H, d, *J* = 8.0, H-5); 8.26 (1H, d, *J* = 8.0, H-4' indole); 8.43 (1H, s, CH=N)

TABLE. 2 (continued)

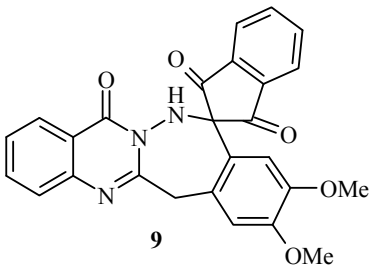
1	2
4e	3.53 and 3.67 (6H, s, 3'- and 4'-OCH_3); 4.13 (2H, s, CH_2); 6.80 (3H, m, H-2',5',6' veratrole); 7.26 (1H, t, *J* = 4.8, H-4' thiophene); 7.53 (1H, t, *J* = 8.0, H-6); 7.70 (2H, m, H-8,5' thiophene); 7.83 (1H, t, *J* = 8.0, H-7); 7.95 (1H, d, *J* = 4.8, H-3' thiophene); 8.14 (1H, d, *J* = 8.0, H-5); 8.95 (1H, s, CH=N)
4f	1.04 (3H, t, *J* = 7.2, $CH_3CH_2CH_2$); 1.77 (2H, sext, *J* = 7.2, $MeCH_2CH_2$); 2.89 (2H, t, *J* = 7.2, $MeCH_2CH_2$); 3.53 and 3.70 (6H, s, 3'- and 4'-OCH_3); 4.13 (2H, s, CH_2); 6.70 (1H, d, *J* = 8.4, H-5' veratrole); 6.81 (1H, s, H-2' veratrole); 6.82 (1H, d, *J* = 8.4, H-6' veratrole); 6.93 (1H, d, *J* = 4.4, H-4' thiophene); 7.46 (2H, m, H-6,3' thiophene); 7.67 (1H, d, *J* = 8.0, H-8); 7.77 (1H, t, *J* = 8.0, H-7); 8.14 (1H, d, *J* = 8.0, H-5); 8.79 (1H, s, CH=N)
4g	2.52 (3H, s, CH_3); 3.60 and 3.73 (6H, s, 3'- and 4'-OCH_3); 4.18 (2H, s, CH_2); 6.33 (1H, d, *J* = 2.8, H-4' furan); 6.69 (1H, d, *J* = 8.4, H-5'); 6.86 (1H, d, *J* = 8.4, H-6'); 6.89 (1H, s, H-2'); 7.05 (1H, d, *J* = 2.8, H-3' furan); 7.46 (1H, t, *J* = 8.0, H-6); 7.67 (1H, d, *J* = 8.0, H-8); 7.75 (1H, t, *J* = 8.0, H-7); 8.15 (1H, d, *J* = 8.0, H-5); 8.52 (1H, s, CH=N)
5a	4.08 (2H, s, OCH_2CH_2O); 4.14 (4H, s, 2-CH_2, OCH_2CH_2O); 6.60 (1H, d, *J* = 8.0, H-5'); 6.70 (1H, d, *J* = 8.0, H-6'); 6.75 (1H, s, H-2'); 7.09 (1H, d, *J* = 4.4, H-3' thiophene); 7.45 (1H, t, *J* = 8.0, H-6); 7.49 (1H, d, *J* = 4.4, H-4' thiophene); 7.65 (1H, d, *J* = 8.0, H-8); 7.75 (1H, t, *J* = 8.0, H-7); 8.14 (1H, d, *J* = 8.0, H-5); 8.96 (1H, s, CH=N)
5b	4.08 (2H, s, OCH_2CH_2O); 4.13 (4H, s, 2-CH_2 and OCH_2CH_2O); 6.60 (1H, d, *J* = 8.0, H-5'); 6.70 (1H, d, *J* = 8.0, H-6'); 6.75 (1H, s, H-2'); 7.46 (1H, t, *J* = 8.0, H-6); 7.60 (1H, s, H-3' thiophene); 7.66 (1H, d, *J* = 8.0, H-8); 7.76 (1H, t, *J* = 8.0, H-7); 7.79 (1H, s, H-5' thiophene); 8.15 (1H, d, *J* = 8.0, H-5); 9.06 (1H, s, CH=N)
6	3.79 and 3.86 (6H, s, 8- and 9-OCH_3); 3.95 (2H, s, H-6); 7.23 (1H, s, H-7); 7.30 (1H, s, H-10); 7.53 (1H, t, *J* = 8.0, H-2); 7.61 (1H, d, *J* = 8.0, H-4); 7.80 (1H, t, *J* = 8.0, H-3); 8.13 (1H, d, *J* = 8.0, H-1); 8.91 (1H, s, CH=N)
7	4.21 (8H, s, OCH_2CH_2O); 4.45 (4H, s, 2-CH_2); 5.58 (2H, br. s, NH); 6.73 (2H, d, *J* = 8.0, H-5'); 7.03 (2H, d, *J* = 8.0, H-6'); 7.08 (2H, s, H-2'); 7.40 (1H, s, H-3' thiophene); 7.53 (1H, s, CH); 7.55 (2H, m, H-6); 7.65 (2H, s, H-5' thiophene); 7.86 (2H, t, *J* = 8.0, H-7); 8.00 (2H, d, *J* = 8.0, H-8); 8.17 (2H, d, *J* = 8.0, H-5)
8a	3.43 and 3.83 (6H, s, 8- and 9-OCH_3); 3.99 and 5.14 (2H, d, *J* = 13.2, H-6); 5.90 (1H, s, H-7); 7.04 (5H, m, NH, H-10,4',5',7' isatin); 7.36 (1H, t, *J* = 8.0, H-6' isatin); 7.49 (1H, t, *J* = 8.0, H-2); 7.67 (1H, d, *J* = 8.0, H-4); 7.80 (1H, t, *J* = 8.0, H-3); 8.05 (1H, d, *J* = 8.0, H-1); 10.45 (1H, s, NH isatin)
8b	3.78 and 5.21 (2H, d, *J* = 13.2, H-6); 4.12 (2H, s, OCH_2CH_2O); 4.18 (2H, s, OCH_2CH_2O); 5.84 (1H, s, H-7); 6.90 (1H, s, H-10); 7.01 (3H, m, H-5',7' isatin, NH); 7.20 (1H, d, *J* = 8.0, H-4' isatin); 7.35 (1H, t, *J* = 8.0, H-6' isatin); 7.46 (1H, t, *J* = 8.0, H-2); 7.62 (1H, d, *J* = 8.0, H-4); 7.77 (1H, t, *J* = 8.0, H-3); 8.05 (1H, d, *J* = 8.0, H-1); 10.58 (1H, s, NH isatin)
9	3.46 and 3.86 (6H, s, 8- and 9-OCH_3); 4.02 and 5.26 (2H, br. s, H-6); 5.04 (1H, br. s, NH); 5.81 (1H, s, H-7); 7.01 (1H, s, H-10); 7.51 (1H, t, *J* = 8.0, H-2); 7.72 (1H, d, *J* = 8.0, H-4); 7.81 (1H, t, *J* = 8.0, H-3); 8.10 (5H, m, H-1, H ninhydrin)
10	1.69 (3H, s, CH_3); 3.07 (COOH exchanges with H_2O); 3.71 and 3.82 (6H, s, 8,9-OCH_3); 4.05 and 4.66 (2H, br. s, H-6); 6.58 (1H, s, NH); 6.80 (1H, s, H-7); 6.96 (1H, s, H-10); 7.42 (1H, t, *J* = 8.0, H-2); 7.56 (1H, d, *J* = 8.0, H-4); 7.71 (1H, t, *J* = 8.0, H-3); 8.09 (1H, s, H-1)
11	1.56 (3H, s, CH_3); 3.14 (2H, s, CH_2); 3.31 and 3.67 (6H, s, 3',4'-OCH_3); 6.60 (1H, s, H-2' veratrole); 6.65 (1H, d, *J* = 8.4, H-6' veratrole); 6.69 (1H, d, *J* = 8.4, H-5' veratrole); 7.51 (3H, m, H-6,3',5'); 7.59 (1H, d, *J* = 8.0, H-8); 7.75 (1H, t, *J* = 8.0, H-4'); 7.82 (1H, t, *J* = 8.0, H-7); 7.96 (2H, d, *J* = 8.0, H-2',6'); 8.14 (1H, d, *J* = 8.0, H-5)

Six-membered heteroaromatic pyridine and quinoline aldehydes react smoothly with N-amino derivatives **1a**,**b** to give diazepines **2m-o**, **3f**,**g**. This reaction is carried out in hydrochloric acid at 80°C for 3-4 h.

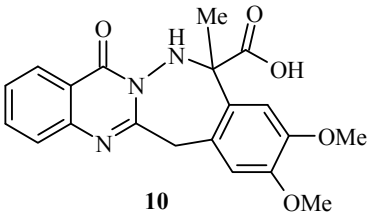
α-Dicarbonyl compounds such as phenylglyoxal, ninhydrin, and isatin give good yields of diazepines **2g**, **8**, and **9**. Ethyl pyruvate hydrolyzes during the reaction such that carboxylic acid **10** is isolated in close to quantitative yield.



8a,b



9



10

8 a R = Me, **b** R = OCH_2CH_2O

Acetophenone and cyclohexanone does not form diazepine products with amine **1a** either in hydrochloric acid or trifluoroacetic acid. Heating a mixture of acetophenone and amine **1a** in trifluoroacetic acid for 24 h gave a 39:61 mixture of 2-(3,4-dimethoxybenzyl)-3-(1-phenylethylidenamino)quinazolin-4(3H)-one (**11**) (*m/z* 414.2 $[M+1]^+$) and starting amine **1a** (*m/z* 312.3 $[M+1]^+$) as indicated by LC/MS and ^{1}H NMR spectroscopy.

Thus, our method for the preparation of 11-R-11,12-dihydroquinazoline[3,2-*c*][2,3]benzodiazepin-14(6H)-ones **2, 3,** and **8-10** under conditions of the Pictet-Spengler reaction yields various alkyl, aryl, hetaryl, and functionalized condensed systems with the 2,3-benzodiazepine fragment.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker Avance II 400 spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The LC/MS spectra were taken on an Agilent 1100 LC/MSD VL spectrometer using atomic pressure chemical ionization (APCI) and a 50×4.6-mm column packed with ZORBAX SB-C18 as the stationary phase. The solvent was 95:5 acetonitrile–water with 0.1% trifluoroacetic acid. Gradient elution was employed. The solvent was introduced at 3.0 ml/min. Characteristics of the products are given in Tables 1 and 2.

11-R-11,12-Dehydroquinazolino[3,2-*c*][2,3]benzodiazepin-14(6H)-ones (General Method). A. For **2a-i**, **k-o**, **3a-g**, and **8-10**. A mixture of corresponding amino derivative **1a** or **1b** (2.5 mmol) and carbonyl compound (2.5 mmol) in hydrochloric acid (10 ml) was stirred at 80-90°C. The reaction time is indicated in Table 1. Freshly-distilled dioxane (1-3 ml) was added for better dissolution of the starting compounds. In the reaction with aliphatic aldehydes, ninhydrin, and ethyl pyruvate, the precipitate of the product is formed in only 10-20 min. After cooling, the mixture is diluted by adding water and neutralized by adding 10% ammonium hydroxide until the mixture became slightly basic (but to pH 4-5 in the preparation of diazepines **2d**,**e**, **3a**,**b**, and **10**). The mixture was left for 1 h. The crystals were filtered off and washed with water.

B. For **2g-o**, **3c-g**, **6**, **8**, and **9**. A mixture of amino derivative **1a** or **1b** (2.5 mmol) and carbonyl compound (2.5 mmol) in trifluoroacetic acid (4 ml) was heated at reflux for 8 h and then treated as in Method A.

Products **2a-c** and **2f** were recrystallized from 2-propanol, **2g,j,** and **9** were recrystallized from DMF, and **2h**,**i**,**k-o**, **3c-g**, **6**, and **8** were recrystallized from acetone or acetone–2-propanol. Diazepine **10** was reprecipitated from aqueous sodium carbonate by adding formic acid.

3-Arylmethylidene-2-(3,4-dimethoxybenzyl)aminoquinazolin-4(3H)-ones (Schiff's bases) 4a-g, 5a,b (General Method). A mixture of corresponding amino derivative **1a** or **1b** (2.5 mmol) and heteroaromatic aldehyde (2.5 mmol) was dissolved in acetic acid (5 ml). The solution was heated at reflux for 5 h, cooled, diluted by adding water, and neutralized by adding 10% ammonium hydroxide until slightly basic. The precipitate was filtered off. Products **4a-d** were crystallized from acetone or acetonitrile–2-propanol, **4e-g** were crystallized from 2-propanol, while **5a**,**b** were crystallized from benzene–hexane. Azomethines **4a-d** were also obtained according to Method B, while **5a**,**b** were also obtained according to Method A.

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