The hydrochloride crystallized from absolute ethanol, m.p. 154–155°.

Anal. Calcd. for $C_9H_9NO_3 \cdot HCl$: C, 50.13; H, 4.67. Found: C, 50.49; H, 4.44.

The picrate crystallized from ethanol, m.p. 146.5–147°.

Anal. Calcd. for $C_9H_9NO_3 \cdot C_6H_3N_3O_7$: C, 44.12; H, 2.96. Found: C, 44.26; H, 3.01.

Condensation of Methyl Nicotinylacetate and N-(2-Bromoethylphthalimide).—A solution of 23.5 g. of N-(2-bromoethylphthalimide) in 15 ml. of freshly fractionated dimethylformamide was added to a near-boiling stirred mixture of 20 g. of dry potassium methyl nicotinylacetate and 40 ml. of dimethylformamide. As soon as the mixture began to reflux, external heating was interrupted since spontaneous ebullition continued for about four minutes. After a total heating time of eight minutes, the brown mixture was cooled, precipitated potassium bromide was filtered, and the filtrate poured into a mixture of 300 ml. of water and 50 ml. of 6 *N* hydrochloric acid. A large amount of insoluble material precipitated. The acid solution was decanted, cleared by ether extraction, and made alkaline with sodium hydroxide solution. After standing at 4° overnight, 7 g. of a semi-solid was filtered and recrystallized from ethanol. The colorless crystals (IX) melted at 144°.

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.54; H, 4.29.

The colorless hydrochloride of IX, prepared in ethereal solution, melted at 145–146° but lost hydrogen chloride readily on recrystallization from ethanol reverting to the base (m.p. 144°). The molten salt resolidified at 152–155°, and then melted again at 190–195°. This salt, the hydrochloride of X, also lost hydrogen chloride on recrystallization from ethanol. The conversion of IX to X was effected best by heating the hydrochloride of m.p. 145–146° at 150–160° for two to three minutes. The molten mass was cooled, dissolved in dilute hydrochloric acid, and the new base X precipitated with sodium carbonate solution. After recrystallization from ethanol it melted at 181°.

Anal. Calcd. for $C_{19}N_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.69; H, 4.66.

The same compound (X) also was obtained in small yield by tedious fractional crystallization of the ethanolic mother liquors of IX. Its m.p. (181°) was not depressed by a sample prepared by isomerization of the hydrochlorides above.

1-(2-Phthalimidoethyl)-3-(methyl carboxyacetyl)-pyridinium Hydroxide (XI).—The aqueous alkaline filtrate of IX (*vide supra*) was neutralized with acetic acid, the precipitated brown oil was extracted into chloroform, and the dried extract was concentrated. Ether was added to the residue and the mixture was cooled at 4° until crystals separated. They were washed with ethyl acetate to remove adherent oil, and recrystallized from ethanol–ether. The water-soluble salt melted at 137–138°.

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90. Found: C, 61.58; H, 4.98.

Methyl α-(2-Phthalimidoethyl)-nicotinylacetate (VIII).—The chloroform–ether mother liquors of the quaternary salt XI were evaporated to dryness, the residue was dissolved in ethyl acetate, the solution was decanted from dark insoluble material, and chromatographed over activated alumina using benzene as an eluent. The colorless product isolated from the first fractions melted at 159–160.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.80; H, 4.68.

Myosmine from VIII.—Since the yield of pure VIII was to small for further work, crude VIII of m.p. 125–140° and its oily, carbonate-soluble mother liquors were refluxed with 6 *N* hydrochloric acid for six hours. The acid solution was evaporated to dryness under reduced pressure, the bases were liberated and extracted into chloroform. Part of the oily residue[18] from the chloroform extract was converted to a picrate which was crystallized from ethanol and from water. It melted at 183° and did not depress the melting point of an authentic sample of myosmine dipicrate.

Anal. Calcd. for $C_{21}H_{16}N_8O_{14}$: C, 41.74; H, 2.67. Found: C, 41.09; H, 2.88.

(18) Fractionation of the oily base gave some 3-acetylpyridine (picrate, m.p. 132–133°, hydrochloride, m.p. 176–177°). The higher boiling fraction was myosmine.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

γ-Pyrones by Isomerizaton. Substituted 3,5-Dibenzyl-4H-pyran-4-ones

BY NELSON J. LEONARD AND DEBABRATA CHOUDHURY

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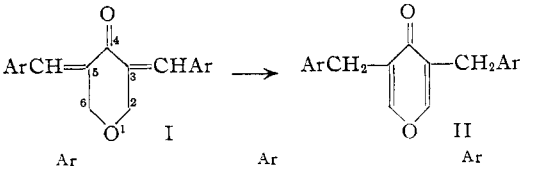
The isomerization of substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones to the correspondingly substituted 3,5-dibenzyl-4H-pyran-4-ones has been effected in boiling diethylene glycol solution using palladium-on-charcoal. The average rate of isoaromatization leading to γ-pyrones appears to be slower than that of the corresponding reaction leading to similarly constituted γ-pyridones and faster than that leading to the tropolones. A series of substituted 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones were synthesized and were found to resist isoaromatization to the corresponding γ-thiapyrones.

As a second general illustration of heterocyclic aromatization using a glycol solvent and palladium-on-charcoal, we turned to the conversion of substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones (I) to the corresponding 3,5-dibenzyl-4H-pyran-4-ones (II). The first general application to the heterocyclic series, the isoaromatization of 1-methyl-3,5-dibenzylidene-4-piperidones to 1-methyl-3,5-dibenzyl-4-pyridones,[1] was based on aromatizations of isocyclic types to 2,6-dibenzylphenols[2] and 3,7-dibenzyltropolones.[3,4] The preparation of the substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones (I) was effected by condensation of the appropriate aldehyde with tetrahydro-4H-pyran-4-one using piperidine acetate in ethanol.[1] These conditions were found to be gen-



a, C_6H_5 e, p-$C_2H_5OC_6H_4$ i, m-$CH_3C_6H_4$
b, p-$CH_3C_6H_4$ f, 3′,4′-$(CH_3O)_2C_6H_3$ j, p-$(CH_3)_2NC_6H_4$
c, p-$(CH_3)_2CHC_6H_4$ g, 3′,4′-$CH_2O_2C_6H_3$ k, p-$NO_2C_6H_4$
d, p-$CH_3OC_6H_4$ h, 2′,3′-$(CH_3O)_2C_6H_3$ l, 1′-$C_{10}H_7$

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(2) E. C. Horning, *J. Org. Chem.*, **10**, 263 (1945).

(3) N. J. Leonard and J. W. Berry, THIS JOURNAL, **75**, 4989 (1953).

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TABLE I

SUBSTITUTED 3,5-DIBENZYLIDENETETRAHYDRO-4H-PYRAN-4-ONES

Tetrahydro-4H-pyran-4-ones, 3,5-di-	I	Yield, %	M.p., °C.	Solvent for recrystn.[a]	Infrared absorption maxima, cm.$^{-1}$[b] Conj. C=O	Conj. C=C and aromatic	Cyclic ether C-O	Misc. (s)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzylidene-	a	58	185[c]	EtOH–$CHCl_3$	1675	1617, 1593, 1500	1105	995	$C_{19}H_{16}O_2$				
(*p*-Methyl)-	b	50	182–184[d]	EtOH–$CHCl_3$	1675	1612, 1587, 1517	1107	995	$C_{21}H_{20}O_2$				
(*p*-Isopropyl)-	c	69	150–151	EtOH	1675	1620, 1590, 1515	1105	997	$C_{25}H_{28}O_2$	83.29	83.08	7.83	7.80
(*p*-Methoxy)-	d	42	178.5[e]	EtOH–$CHCl_3$	1671	1604, 1550, 1520	1110	1175, 995, 835	$C_{21}H_{20}O_4$	74.98	74.76	5.99	6.11
(*p*-Ethoxy)-	e	56	190–191	EtOH–$CHCl_3$	1677	1608, 1550, 1517	1105	995, 709	$C_{23}H_{24}O_4$	75.80	75.95	6.64	6.74
(3′,4′-Dimethoxy)-	f	58	180–181	EtOH–$CHCl_3$	1675	1622, 1610, 1522	1110	1030, 1007	$C_{23}H_{24}O_6$	69.68	69.49	6.10	5.92
(3′,4′-Methylenedioxy)-	g	55	214–216	MeOH–$CHCl_3$	1675	1605, 1582, 1505	1104	1000	$C_{21}H_{16}O_6$	69.22	69.27	4.43	4.00
(2′,3′-Dimethoxy)-	h	50	113	EtOH	1680	1625, 1600, 1507	1095	1487, 1005	$C_{23}H_{24}O_6$	69.68	69.50	6.10	6.14
(*m*-Methyl)-	i	33	101–102	EtOH	1680	1625, 1595, 1520	1110	1495, 997	$C_{21}H_{20}O_2$	82.86	82.83	6.62	6.63
(*p*-Dimethylamino)-	j	42	288–289	DMF	1660	1590, 1530	1100	995	$C_{23}H_{26}N_2O_2$	76.21	76.35	7.23	7.35[f]
(*p*-Nitro)-	k	60	272–273	DMF	1684	1625, 1600, 1523	1107	1200, 1100, 1000	$C_{19}H_{14}N_2O_6$	62.29	62.52	3.85	4.17[g]
1′-Naphthylidene-	l	58	203.5–204.5	EtOH	1678	1618 1515	1104	995	$C_{27}H_{20}O_2$	86.14	86.21	5.36	5.66

[a] Crystal form, uniformly needles; color, yellow except Ij, which is orange. [b] Spectra determined as 5% solutions in chloroform, except Ic, g, j, k, which were determined as mulls. [c] Reported[5,6] 185°. [d] Reported[5] 186°. [e] Reported[6] 179–180°. [f] Calcd.: N, 7.73. Found: N, 7.76. [g] Calcd.: N, 7.65. Found: N, 7.94.

erally applicable (Table I), whereas aqueous ethanolic alkali, which had been used previously for the synthesis of Ia, b and d,[5,6] was not satisfactory for the preparation of certain other members of this series, notably Ij and k.

The 3,5-dibenzylidenetetrahydro-4H-pyran-4-one structures I were indicated as correct for this series on the basis of analysis, yellow color, intense color reaction with sulfuric acid,[7] infrared absorption spectra[1] (Table I), and the ultraviolet absorption spectrum of the parent compound (Ia) in the series. Ultraviolet maxima were recorded for Ia in 95% ethanol at 330 mμ (log ε 4.43) and at 233 mμ (log ε 4.11), comparable to those observed[1] for 1-methyl-3,5-dibenzylidene-4-pyridone and 2,6-dibenzylidenecyclohexanone.

The possibility of isomerization of I to II seemed reasonable on the basis of the stated analogies and the considerable body of physical and chemical evidence supporting the postulate of Arndt[8,9] as to the aromatic character of the γ-pyrone nucleus. In our investigation of the intended aromatization using palladium-on-carbon to facilitate the hydrogen exchange, diethylene glycol (b.p. range 244–248°) was selected as the most favorable solvent since 3,5-dibenzylidenetetrahydro-4H-pyran-4-one (Ia) was recovered from refluxing ethylene glycol[1] and suffered decomposition in refluxing triethylene glycol.[3] Diethylene glycol possesses the advantage of the other glycols in facilitating separation of the reaction product from the catalyst. The colorless solid obtained from Ia following heating with palladium-on-carbon in refluxing diethylene glycol was isomeric with Ia and was assigned the structure IIa, 3,5-dibenzyl-4H-pyran-4-one, on the following evidence: the absence of color, the failure to give a color reaction with sulfuric acid, an infrared spectrum indicative of a modified carbonyl group and a modified cyclic ether group (Table II), and a striking alteration in ultraviolet absorption spectrum from that exhibited by Ia. The new $C_{19}H_{16}O_2$ compound exhibited an ultraviolet maximum at 260 mμ (log ε 4.07) and a possible maximum near 210 mμ (log ε 4.47). Similar chemical and physical evidence, as indicated in Table II, permitted the structural assignment of all of the isomerization products as substituted 4H-pyran-4-ones (IIa-g,l). As a final check on the assigned structures, one of the compounds in the series, 3,5-di-(*p*-methylbenzyl)-4H-pyran-4-one (IIb), was converted, in nearly quantitative yield, to the known 1-methyl-3,5-di-(*p*-methylbenzyl)-4-pyridone[1] by treatment with ethanolic methylamine in a sealed tube. This facile conversion reaction is typical of γ-pyrones.[10–12]

In the interest of comparing the facility of isoaromatization in the tetrahydro-4H-1-thiapyran-4-

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TABLE II

SUBSTITUTED 3,5-DIBENZYL-4H-PYRAN-4-ONES

4H-Pyran-4-ones, 3,5-di-	II	Yield, %	Parts of catalyst[a]	Reflux time, hr.[b]	M.p., °C.	Crystal form[c]	Infrared absorption maxima, cm.$^{-1}$[d] Pyrone C=O	Aromatic	Pyrone ether =C-O-C=	Misc. (s)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzyl-	a	25	0.1	2.0	68.5	Plates[e]	1652	1625, 1500	1325	3000, 1375, 700	$C_{19}H_{16}O_2$	82.58	82.40	5.84	5.69
(*p*-Methyl)-	b	⩽100	.1	3.5	110	Plates[e]	1652	1617, 1520	1330	3000, 1435, 1355	$C_{21}H_{20}O_2$	82.86	82.56	6.62	6.70
(*p*-Isopropyl)-	c	33	.1	0.4	74.5–75.5	Ndls.[f]	1650	1615, 1515	1325	2990, 1070	$C_{25}H_{28}O_2$	83.29	82.89	7.83	8.13
(*p*-Methoxy)-	d	90	.1	3.0	68–69	Plates[e]	1651	1615, 1517	1330	3000, 1355	$C_{21}H_{20}O_4$	74.99	75.05	5.99	6.10
(*p*-Ethoxy)-	e	80	.3	1.0	103–104	Ndls.[g]	1658	1622, 1522, 1490	1335	3000, 1405	$C_{23}H_{24}O_4$	75.80	75.87	6.64	6.77
(3′,4′-Dimethoxy)-	f	80	.3	0.7	118.5–119.5	Plates[g]	1652	1615, 1518, 1475	1330	3000, 1140	$C_{23}H_{24}O_6$	69.68	69.56	6.10	6.07
(3′,4′-Methylenedioxy)-	g	88	.6	< .1	138–139	Ndls.[h]	1650	1620, 1510	1337	1250, 925, 800	$C_{21}H_{16}O_6$	69.22	69.18	4.43	4.53
1′-Naphthyl-	I	96	.4	< .1	154–155	Ndls.[i]	1658	1615, 1520	1335	3020, 1355, 1175	$C_{27}H_{20}O_2$	86.14	85.85	5.36	5.55

[a] Catalyst (g.) per g. of I. [b] Diethylene glycol as solvent, except for IId, where ethylene glycol was employed. [c] All colorless. [d] Spectra determined as 5% solutions in chloroform, except IIg, which was determined as a mull. [e] From petroleum ether. [f] Ethanol at Dry Ice temperature. [g] Hexane. [h] Hexane–ethanol. [i] Ethanol–chloroform.

TABLE III

SUBSTITUTED 3,5-DIBENZYLIDENETETRAHYDRO-4H-1-THIAPYRAN-4-ONES

Tetrahydro-4H-1-thiapyran-4-ones, 3,5-di-	III	Yield, %	M.p., °C.	Crystal[a] form	Infrared absorption maxima, cm.$^{-1}$[b] Cong. C=O	Conj. C=C and aromatic	Thioether C-S[13]	Misc.(s)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzylidene	a	76	150–151[c]	Plates[d]	1670	1615, 1500		1275, 1140	$C_{19}H_{16}OS$	78.05	77.73	5.52	5.66[g]
(*p*-Methyl)-	b	75	196–197	Ndls.[d]	1665	1605, 1585, 1512	735, 720	1320, 1200, 1189	$C_{21}H_{20}OS$	78.72	78.49	6.29	6.35
(*p*-Isopropyl)-	c	31	159.5	Ndls.[d]	1662	1605, 1510		1280, 1140, 1195	$C_{25}H_{28}OS$	79.75	79.57	7.50	7.54
(*p*-Methoxy)-	d	92	183.5–184.5	Ndls.[e]	1660	1600, 1570, 1515	740, 720	1315, 1305	$C_{21}H_{20}O_3S$	71.58	71.86	5.72	5.80
(3′,4′-Dimethoxy)-	f	67	165–166	Ndls.[e]	1657	1607, 1585, 1525	735, 725	1335	$C_{23}H_{24}O_5S$	66.97	66.76	5.86	5.89
(*p*-Dimethylamino)-	j	77	256–257	Ndls.[e]	1648	1615, 1590, 1525	725, 707	1370	$C_{23}H_{26}N_2OS$	72.99	73.18	6.92	6.94[h]
(*p*-Nitro)-	k	77	224–225	Plates[f]	1675	1595, 1520	705	1350	$C_{19}H_{14}N_2O_5S$	59.69	60.06	3.69	4.07
1′-Naphthylidene-	l	75	191.5–192.5	Ndls.[e]	1660	1605, 1580, 1510	725	1285, 1142	$C_{27}H_{20}OS$	82.63	82.38	5.14	5.39

[a] All yellow or light yellow, except IIIj, which is orange. [b] Spectra determined as mulls, except IIIa and IIIc, which were determined as 5% solutions in chloroform. [c] Reported[14] 149–151°. [d] From ethanol. [e] Ethanol–chloroform. [f] Acetone–chloroform. [g] Calcd.: S, 10.96. Found: S, 10.82. [h] Calcd.: N, 7.40. Found: N, 7.42.

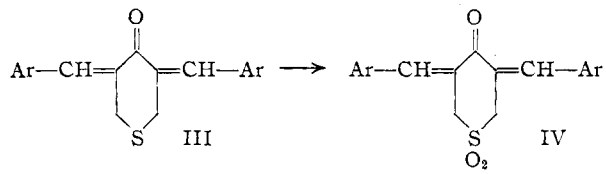
TABLE IV

SUBSTITUTED 3,5-DIBENZYLIDENETETRAHYDRO-4H-1-THIAPYRAN-4-ONE 1,1-DIOXIDES

Tetrahydro-4H-1-thiapyran-4-one 1,1-dioxides, 3,5-di-	IV	Yield, %	M.p., °C.[a]	Infrared absorption maxima, cm.$^{-1}$[b] Conj. C=O	Conj. C=C and aromatic	Sulfone regions[19]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzylidene-	a	89	198–199	1668	1625, 1602, 1500	1352, 1345, 1325, 1225, 1195	$C_{19}H_{16}O_3S$	70.36	70.35	4.98	5.21
(*p*-Methyl)-	b	73	197–198	1670	1618, 1601, 1515	1340, 1322, 1275, 1190, 1185	$C_{21}H_{20}O_3S$	71.58	71.72	5.72	5.98
(*p*-Isopropyl)-	c	80	167–168	1670	1625, 1607, 1520	1350, 1325, 1305, 1230, 1140	$C_{25}H_{28}O_3S$	73.51	73.31	6.91	7.05
(*p*-Methoxy)-	d	64	186–187	1660	1595, 1565, 1515	1335, 1320, 1260, 1180, 1140	$C_{21}H_{20}O_5S$	65.61	65.47	5.24	5.02
(*p*-Nitro)-	k	95	233.5–234.5	1682	1616, 1600, 1520	1350, 1326, 1305, 1230, 1195	$C_{19}H_{14}N_2O_7S$	55.08	55.04	3.41	3.65[c]
1′-Naphthylidene-	l	86	231–232	1672	1600, 1535	1320, 1310, 1270, 1210, 1195	$C_{27}H_{20}O_3S$	76.40	76.33	4.70	4.80

[a] All bright yellow needles (except IVk, plates) from glacial acetic acid. [b] Spectra determined as Nujol mulls. [c] Calcd.: N, 6.76. Found: N, 6.55.

one series with that in the tetrahydro-4H-pyran-4-one series, we synthesized the substituted 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones (III) listed in Table III. The most satisfactory general method proved to be the condensation of the appropriate aldehyde with tetrahydro-4H-1-thiapyran-4-one using piperidine acetate in refluxing ethanol. The structure assignments were based, as in the case of the oxygen analogs, on elemental



analysis, the yellow color of the products, the intense color reaction with sulfuric acid, the infrared absorption spectra (Table III), and the ultraviolet absorption spectrum of the parent compound (IIIa) in the series.

In the light of the successful isoaromatizations realized for tropolones, phenols, γ-pyridones and γ-pyrones, it was logical to assume the possibility of converting the substituted 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones (III) to the correspondingly substituted 3,5-dibenzyl-4H-1-thiapyran-4-ones. The aromatic character of the 4H-1-thiapyran-4-ones was realized some years ago by Arndt and others.[15-17] Attempts at isomerization of representative compounds (III) using palladium-on-carbon in refluxing ethylene glycol or diethylene glycol resulted in the isolation of starting material, whereas refluxing triethylene glycol resulted in extensive decomposition of III and afforded none of the corresponding 4H-1-thiapyran-4-one. Realizing that catalytic desulfurization might be one of the reactions competing with the intended isomerization, we turned to the use of cobalt polysulfide, which has found employment as a sulfactive catalyst.[18] Under a variety of conditions it was ineffective in bringing about the isomerization of compounds of type III, and extensive decomposition occurred when refluxing triethylene glycol constituted the reaction medium. A number of methods[4] other than catalytic were equally unsuccessful. The conclusion is reached that the isomerization of the selected 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones to the corresponding 3,5-dibenzyl-4H-1-thiapyran-4-ones, if it occurs, proceeds at a rate which competes unfavorably with more destructive reactions. It is clear that the rate of isomerization of III must be slower than that of the isomerization of compounds of type I to γ-pyrones II, which in turn is slower than that of the corresponding reaction leading to similarly constituted γ-pyridones.[1]

The sulfones were prepared from the compounds in series III and were characterized as having structures indicated by IV on the basis of their physical properties, including infrared absorption spectra (Table IV). The parent compound in this series, 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-one 1,1-dioxide (IVa), exhibited ultraviolet absorption maxima at 310 mμ (log ε 4.31) and 233 mμ (log ε 4.13), slightly shifted from those of 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-one (IIIa), 300 mμ (log ε 4.21) and 230 mμ (log ε 4.21), as determined in 95% ethanol. The sulfone series (IV) resisted isomerization, as would be expected.[15,17]

The synthetic utility of the present work lies in the generally applicable method of making substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones and 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones (and their 1,1-dioxides), and the facile conversion of the former into substituted 4H-pyran-4-ones which would be difficult to make by other means.

Experimental[20]

Tetrahydro-4H-pyran-4-one.—This compound was prepared by the hydrogenation of 4H-pyran-4-one (γ-pyrone),[21] according to the directions of Cornubert, Delmas, Monteil and Viriot,[5] using freshly prepared Raney nickel at 25°; b.p. 70–72° (18 mm.), $n^{20}D$ 1.4594 (reported[5] b.p. 60–61° (13.5 mm.), $n^{12.5}D$ 1.4545).

Substituted 3,5-Dibenzylidenetetrahydro-4H-pyran-4-ones (I).—Compounds Ia, b and d were prepared as described previously,[5,6] using aqueous alcoholic alkali as the condensing agent for tetrahydro-4H-pyran-4-one and the appropriate aldehyde. The other compounds in the series were prepared by the method which is typified in the procedure for 3,5-di-(*p*-isopropylbenzylidene)-tetrahydro-4H-pyran-4-one (Ic). A solution of 3 g. (0.02 mole) of *p*-isopropylbenzaldehyde and 1 g. (0.01 mole) of tetrahydro-4H-pyran-4-one in 30 ml. of absolute ethanol, to which was added 2 ml. of piperidine and 1 ml. of glacial acetic acid, was heated under reflux for 3 days. The cooled solution deposited long yellow needles. The properties of Ic and the other compounds in the series are given in Table I. Each of the condensation products gave an intense color reaction with sulfuric acid, varying with the individual compounds from red to deep violet.

Aromatization to Substituted 3,5-Dibenzyl-4H-pyran-4-ones (II) with Palladium-on-carbon.—Ethylene glycol[1] was a satisfactory solvent for the catalytic isomerization of Id to IId. Diethylene glycol was found to be preferable in most other cases. The general method of isoaromatization can be illustrated as follows. A mixture of 0.5 g. of 3,5-di-(*p*-ethoxybenzylidene)-tetrahydro-4H-pyran-4-one (Ie), 0.15 g. of 10% palladium-on-carbon catalyst[22] and 15 ml. of diethylene glycol was heated under reflux for one hour. The solution was filtered, and the catalyst was washed with a small amount of hot diethylene glycol. Water was added to the filtrate, and the cooled mixture was extracted with ether. The combined ether extracts were dried, and the ether was evaporated. The residue was purified by recrystallization or by chromatography followed by recrystallization. Low yields may reflect difficulty of purification. The optimum conditions for each conversion are given in Table II, along with the properties of each 4H-pyran-4-one product. Compounds IIh, i, j and k could not be obtained in pure form by this method.

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(21) We wish to thank Eli Lilly and Company, Indianapolis, Ind., for a generous gift of γ-pyrone.

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1-Methyl-3,5-di-(*p*-methylbenzyl)-4-pyridone from 3,5-Di-(*p*-methylbenzyl)-4H-pyran-4-one.[10-12]—A mixture of 0.5 g. of 3,5-di-(*p*-methylbenzyl)-4H-pyran-4-one and 0.5 g. of methylamine in 6 ml. of absolute methanol was heated in a sealed tube at 160° for 14 hours. The reaction mixture was filtered, yielding 0.5 g. (97%) of colorless needles, m.p. 229.5–233°, identical with 1-methyl-3,5-di-(*p*-methylbenzyl)-4-pyridone, m.p. 231–234°.[1] The melting point was improved by recrystallizing each sample from ethanol as colorless needles, m.p. 236–237°.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.23; H, 7.30; N, 4.41. Found: C, 83.22; H, 7.38; N, 4.21.

Substituted 3,5-Dibenzylidenetetrahydro-4H-1-thiapyran-4-ones (III).—Condensation of various aldehydes with tetrahydro-4H-1-thiapyran-4-one[23-25] was carried out more favorably with piperidine acetate in ethanol, as in the general method for the oxygen analogs, than with aqueous ethanolic alkali, which had been used previously.[14] The results are given in Table III.

Substituted 3,5-Dibenzylidenetetrahydro-4H-1-thiapyran-4-one 1,1-Dioxides (IV).—The sulfones IV were made from the corresponding sulfides III in the usual manner. A mixture of 2 g. of the substituted 4H-1-thiapyran-4-one (III), 20 ml. of glacial acetic acid and 3 ml. of 30% hydrogen peroxide was heated under reflux for 10 minutes. The product separated on cooling. The sulfone derivatives are listed in Table IV.

Reaction of 3,5-Dibenzylidenetetrahydro-4H-1-thiapyran-4-one 1,1-Dioxide with Hydrogen Bromide in Acetic Acid.—To a solution of 20 ml. of glacial acetic acid saturated with hydrogen bromide at 25° and containing 0.1 g. of benzoyl peroxide was added 0.5 g. of 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-one 1,1-dioxide. The orange-colored solution was maintained at 60° for 22 hours, after which time it had become dark red. Dilution to 100 ml. with water and refrigeration caused the separation of a colorless solid, m.p. 219–220°. Recrystallization from acetic acid gave colorless needles, m.p. 220–220.5°, which contained bromine.

Anal. Calcd. for $C_{19}H_{18}Br_2O_3S$: C, 46.93; H, 3.72. Found: C, 47.11; H, 4.11.

The infrared spectrum (mull) indicated the presence of unconjugated carbonyl (1725 cm.$^{-1}$) along with maxima typical of phenyl and sulfone groupings. The product could not be dehydrobrominated readily. Neither possible structure, 3,5-di-(α-bromobenzyl)-tetrahydro-4H-1-thiapyran-4-one 1,1-dioxide or 3,5-dibenzyl-3,5-dibromotetrahydro-4H-1-thiapyran-4-one 1,1-dioxide, has been rigorously excluded for this product.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Synthesis of Inosamine and Inosadiamine Derivatives from Inositol Bromohydrins[1]

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The m.p. 240° diastereoisomer of 6-bromoquercitol pentaacetate reacted with ammonia in hot dioxane to give small yields of two diastereoisomeric inosamines, isolated as the hexaacetyl derivatives, m.p. 157° and 280°. The former diastereoisomer appears to be new, and the latter was found to be identical with the *meso*-(1,3,5) ("SB" or "III") inosamine derivative whose preparations from *meso*-(1,3,5)- or "*scyllo*"-inosose, and from 6-deoxy-6-nitro-D-glucose, had previously been reported. Two isomers (m.p. 225° and 130°) of dibromocyclohexanetetrol tetraacetate on similar amination gave two hexaacetylstreptamine diastereoisomers of m.p. 303° and 173°, possibly but not certainly identical with similar isomers previously prepared in other laboratories by different procedures and isolation techniques.

During the last decade much interest has been shown in the diaminocyclohexanetetrols or inosadiamines,[3] and their simpler monoamino analogs, the inosamines. The original stimulus to this interest was the establishment of the diastereoisomer XVI as a component of the antibiotic streptomycin.[4-7] The natural substance XVI is designated streptamine.[5,6] In this communication the words *o*-inosadiamine, *m*-inosadiamine and *p*-inosadiamine will be employed as generic names for the various diastereoisomers of 5,6-, 4,6- and 3,6-diaminocyclohexanetetrol, respectively. The inosadiamine and inosamine ring numbering here used (Figs. 1 and 2) is a departure from the previous usage found in most articles on streptomycin derivatives, but is in conformity with *Chemical Abstracts* practice, which regards the hydroxyl group as the principal function in any amino alcohol. The term inosamine, proposed by Carter and co-workers,[8] has been widely adopted as a generic name for the 20 predictable diastereoisomers of 6-amino-1,2,3,4,5-cyclohexanepentol. Six of these diastereoisomers have been reported previously,[8-13b] and one additional is now recorded herein (VII, Table I). The inosamines are stable, colorless, crystalline solids with poor melting points, and are best characterized as the hexaacetyl derivatives. Even these are best further delineated by their X-ray powder diffraction lines and such data are recorded herein for the substances with which this Laboratory was concerned.

(1) One of a series of articles on streptomycin chemistry by M. L. Wolfrom and co-workers; paper IX on Cyclitols by G. E. McCasland and co-workers, previous communication G. E. McCasland and J. M. Reeves, THIS JOURNAL, **77**, 1812 (1955).

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