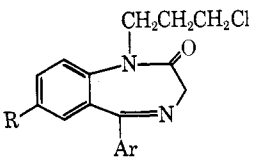
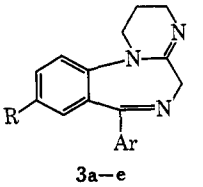
TABLE I

1-SUBSTITUTED 1,4-BENZODIAZEPINES



2a–e



3a–e

Compd	R	Ar	Method	Recrystn solvent[a]	Mp, °C	Yield, %	Formula	Analyses[b]
2a	Cl	C_6H_5	I	A–B	87–90	72.3	$C_{18}H_{16}Cl_2N_2O$	C, H
2b	Cl	*o*-FC_6H_4	I	A–B	86–89	49.5	$C_{18}H_{15}Cl_2FN_2O$	C, H
2c	Br	2-Pyridyl	I	A–C	103–106	41.9	$C_{17}H_{15}BrClN_3O$	C, H, N
2d	CF_3	C_6H_5	I	A–C	118–123	50.4	$C_{19}H_{16}ClF_3N_2O$	C, H, N
2e[c]	H	C_6H_5	I					
3a	Cl	C_6H_5	II	F–C	155–157		$C_{18}H_{16}ClN_3$	C, H, N
3a·HI				D	270–275	49.3	$C_{18}H_{16}ClN_3$·HI	C, H
3b	Cl	*o*-FC_6H_4	II	E–F	161.5–163		$C_{18}H_{15}ClFN_3$	C, H, N
3b·HI				D–A	286–289	64.7	$C_{18}H_{15}ClFN_3$·HI	C, H, N
3c	Br	2-Pyridyl	II	F	178–181		$C_{19}H_{15}BrN_4$	C, H, N
3c·HI				D	272–275	34.5	$C_{17}H_{15}BrN_4$·HI	C, H, N
3d	CF_3	C_6H_5	II	F	179–181		$C_{19}H_{16}F_3N_3$	C, H, N
3d·HI				D	278–282	38.4	$C_{19}H_{16}F_3N_3$·HI	C, H
3e	H	C_6H_5	II	A	143–145		$C_{18}H_{17}N_3$	C, H, N
3e·HI				D	293–295	52.3	$C_{18}H_{17}N_3$·HI	C, H, N

[a] A = Et_2O, B = petroleum ether (bp 30–60°), C = hexane, D = EtOH, E = C_6H_6, F = cyclohexane. [b] Acceptable analytical results were obtained for the elements indicated. [c] The isolation of this compound gave a 40.4% yield of an oil which was converted to **3e** without characterization.

Experimental Section[5]

1-(3-Chloropropyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-ones (2a–e). **Method** I.—The appropriate 1,4-benzodiazepin-2-one (**1a–e**)[6] was dissolved in a mixture of DMF and THF (1:1) and this solution, under dry N_2, was treated with excess (10–25%) $NaNH_2$. The mixture was stirred for 2 hr at 50° and was then treated with a threefold excess of 1-bromo-3-chloropropane and was stirred overnight. The reaction mixture was poured into ice water and extracted with CH_2Cl_2 which was dried and evaporated to dryness. The residue was chromatographed on Woelm neutral alumina (Activity 1) on which the product was always less strongly adsorbed than the starting material.

1,2,3,5-Tetrahydropyrimido[1,2-*a*][1,4]benzodiazepines (3a–e). **Method** II.—A mixture of the appropriate 1-(3-chloropropyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2a–e**), 1 equiv of KI, and excess NH_3 in EtOH was heated at 75° for 10 hr with shaking in a sealed container. The reaction mixture was filtered, removing KI, and the filtrate was concentrated *in vacuo* to a residue which was recrystallized from EtOH to give the product as the hydriodide salt. These salts were neutralized in the usual manner to give the crystalline free bases.

8-Chloro-6-(2-fluorophenyl)-1,2-dihydro-4H-imidazo[1,2-*a*][1,4]benzodiazepine (4).—A solution of 5.0 g (15 mmol) of 1-(2-aminoethyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one[7] in 100 ml of EtOH was heated for 24 hr at reflux. The solvent was removed *in vacuo* to give a gum which was then triturated with cyclohexane to give 3.9 g (82.5%) of crystals, mp 174–177°. Recrystallizations from CH_2Cl_2–cyclohexane gave pure product as colorless needles, mp 175–177°. *Anal.* ($C_{17}H_{13}ClFN_3$) C, H, N, Cl, F.

Acknowledgments.—We are indebted to Mr. S. Traiman for the infrared spectrophotometric determinations and to Dr. Al Steyermark and his staff for the microanalyses.

(5) All melting points were determined on a hot stage microscope and are corrected.

(6) Compound **1a**: L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); **1b, e**: L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *ibid.*, **27**, 2788 (1962), **1c**: R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964); **1d**: G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

(7) J. V. Earley, R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Med. Chem.*, **11**, 774 (1968).

Some 4H,12H-Pyrano[2,3-*a*]phenoxazin-4-ones

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Derivatives of phenoxazine[2-5] and γ-pyrone[6-11] are reported to possess marked physiological activity. It was thought desirable to synthesize some 4H,12H-pyrano[2,3-*a*]phenoxazine-4-ones which will incorporate both phenoxazine and γ-pyrone moieties in its molecule, for biological evaluation.

Experimental Section[12]

8-Amino-7-hydroxy-2-methylchromone was prepared by reducing 8-nitro-7-hydroxy-2-methylchromone[13] with sodium hy-

(1) Cleveland Clinic, Cleveland, Ohio.

(2) (a) M. L. Crossley, P. F. Dreisbach, C. M. Hofmann, and R. P. Parker, *J. Am. Chem. Soc.*, **74**, 573 (1952); (b) M. L. Crossley, R. J. Turner, C. M. Hofmann, P. F. Dreisbach, and R. P. Parker, *ibid.*, **74**, 578 (1952); (c) M. L. Crossley, C. M. Hofmann, and P. F. Dreisbach, *ibid.*, **74**, 584 (1952); (d) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499 (1953).

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(4) M. R. Lewis, P. P. Goland, and H. A. Sloviter, *Cancer Res.*, **9**, 736 (1949).

(5) P. N. Craig, U. S. Patent 2,947,745 (1960).

(6) E. Kohlstaedt and K. H. Klingler, German Patent 1,018,874 (1957).

(7) J. Klosa, *J. Prakt. Chem.*, **22**, 259 (1963).

(8) R. H. Highby, *J. Am. Pharm. Assoc.*, **32**, 74 (1943).

(9) H. Nakamura, T. Ota, and G. Fukuchi, *J. Pharm. Soc. Japan*, **56**, 68 (1936).

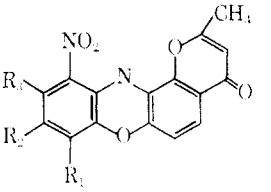
(10) V. V. S. Murti, N. V. S. Rao, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **25A**, 22 (1947); V. V. S. Murti, L. R. Row, and T. R. Seshadri, *ibid.*, **27A**, 33 (1948); T. R. Seshadri and N. Vishwanadham, *ibid.*, **25A**, 337 (1947).

(11) P. DaRe, L. Verlicchi, and I. Setnikar, *J. Org. Chem.*, **25**, 1097 (1960).

(12) Melting points are taken in capillaries and are uncorrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

(13) C. B. Thanawalla, S. Seshadri, and P. L. Trivedi, *J. Indian Chem. Soc.*, **36**, 674 (1959).

TABLE I
4H,12H-PYRANO[2,3-*a*]PHENOXAZIN-4-ONES



No.	Derivative of benzene	R_1	R_2	R_3	Yield, %	Mp, °C	Formula[a]
1	1-Chloro-2,4,6-trinitro-	H	NO_2	H	80	305	$C_{16}H_9N_3O_7$
2	1-Chloro-2,4,6-trinitro-5-methyl-	CH_3	NO_2	H	70	290	$C_{17}H_{11}N_3O_7$
3	1,2,3-Trichloro-4,6-dinitro-	Cl	NO_2	H	75	295	$C_{16}H_6ClN_3O_7$
4	1,4-Dichloro-2,6-dinitro-	H	Cl	H	65	275	$C_{16}H_8ClN_2O_5$
5	1,2,5-Trichloro-4,6-dinitro-	H	NO_2	Cl	70	260	$C_{16}H_5ClN_3O_7$
6	1,2-Dichloro-4,6-dinitro-5-methyl-	H	NO_2	CH_3	72	250	$C_{17}H_{11}N_3O_7$

[a] All compounds were analyzed for C, H, N.

disulfite, following the procedure of Kaufman, *et al.*,[14] mp 254–255° (EtOH).

Anal. Calcd for $C_{16}H_8NO_3$: 62.82; H, 4.71; N, 7.32. Found: C, 62.80; H, 4.91; N, 7.40.

(14) K. D. Kaufman, W. E. Russey, and L. R. Worden, *J. Org. Chem.*, **27**, 875 (1962).

General Method for the Preparation of 4H,12H-Pyrano[2,3-*a*]phenoxazin-4-ones.—To a solution of a halogenonitrobenzene (0.01 mole), 8-amino-7-hydroxy-2-methylchromone (0.01 mole), and EtOA was added NaOAc (10 ml, 2 *N*) under stirring. The mixture was refluxed for 2 hr. After cooling, the pyranophenoxazin-4-ones were filtered, washed (H_2O), and crystallized from AcOH. Compounds prepared in this way are listed in Table I.

Book Reviews

Progress in Biochemical Pharmacology. Volumes 2 and 3. Drugs Affecting Lipid Metabolism. Parts I and II. Edited by D. KRITCHEVSKY, R. PAOLETTI, and D. STEINBERG. S. Karger A. G., Basel, Switzerland, 1967. xii + 520 pp and 532 pp, respectively. 17.5 × 24.5 cm. $29.80 each volume.

From the title of this series, Progress in Biochemical Pharmacology, one would expect its content to constitute a review series. Somewhat surprisingly, this pair of volumes edited by three noted authorities in the field of lipid metabolism is rather a compilation of the papers presented at the Second International Symposium on Drugs affecting Lipid Metabolism held in Milan, Sept 1965. This is consistent with the contents of Volumes 1 and 4 (in preparation) which cover Symposia on Radioactive Drugs and Atherosclerosis, respectively.

The table of contents enumerates titles of 54 and 56 papers, respectively, and the names of an array of distinguished scientists. These papers are grouped into categories of (Volume 2) Cholesterol and Atherosclerosis, Plasma Triglycerides and Lipoproteins, Drugs Affecting Plasma Lipids, and (Volume 3) Fatty Acids, Prostaglandins, Free Acid Mobilization, Free Fatty Acid and Triglyceride Transport, and Liposoluble Vitamins. Each of these sections is "introduced by a paper presenting recent developments in basic biochemistry as a background for subsequent papers on drug effects." This provides an exceedingly satisfactory format because of the particular excellence of these discussions. The authors of these papers, W. L. Holmes, N. W. DiTullio, G. Schettler, M. F. Oliver, F. Lynen, B. Samuelsson, D. Steinberg, A. Bizzi, S. Garattini, and D. S. Goodman, are to be congratulated for the particular excellence and lucidity of their presentations.

A general point which merits reflection and discussion by research scientists is the whole question of archival-type publication of symposium proceedings. A complete, as opposed to a selective, record of special lectures at a symposium comprising approximately 100 papers can indeed gather a large amount of current information on a specific subject into one compilation. However, these presentations which are often cited later in the sense of published work are categorized as such without undergoing the usual, critical refereeing process practiced by standard journals. It may be that careful dissemination of invitations to participants and/or subsequent open discussion, carefully recorded in the proceedings, sometimes covers this point. Still, in this instance, over 100 sets of authors required selection. For the minority of papers for which discussion was indeed recorded there was an average of less than one page of commentary.

In many instances, the work either was or will have to be republished with complete experimental data thus leading to a partial or completely duplicate publication or else leave unrecorded many of the details so helpful to later workers. On the whole, it appears that the policy of the Sixth International Congress of Biochemistry or the IUPAC meetings of recording a few unique and rather extensive plenary lectures by outstanding figures is more satisfactory. It provides a rapid and perceptive general review of milestones for other workers in the field while leaving to normal publication channels the vast majority of first class but more standard papers. If an archival record is desired, then the time factor (a year at most) should be stressed and a complete record of all open postpaper discussion should be kept, thereby best approximating actual attendance at the meeting.

In summary, these books present an apparently complete record of an interesting and meritorious symposium held in Sept 1965. By the time this review appears in mid 1968, on the heels of the next scheduled International Symposium on Drugs affecting Lipid Metabolism, some of this work will have been published in standard journals. If one has an intense and continuing interest in this area and/or a library budget which can carry the $59.60 cost of the set, then its purchase can be recommended. However, one can speculate that (a) a rapidly published, soft-covered, photo-offset set of volumes or (b) a selected presentation of plenary lectures followed by a listing of other speakers and their abstracts, either at a reduced price, would command a significantly greater response than these books are likely to receive.

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