Department Research, Ethylene Research, and Edgar C. Britton Research Laboratories for helpful discussion and suggestions during the course of this work. We also wish to thank Professor M. Calvin for his initial suggestion on the use of sulfonium compounds and Mr. John Kadlabitsky for laboratory assistance.

Heterocycles from Keto Acids with Amino Alcohols, Diamines, and Mercaptoamines

PAUL AEBERLI AND WILLIAM J. HOULIHAN

Sandoz Pharmaceuticals, Hanover, New Jersey 07936

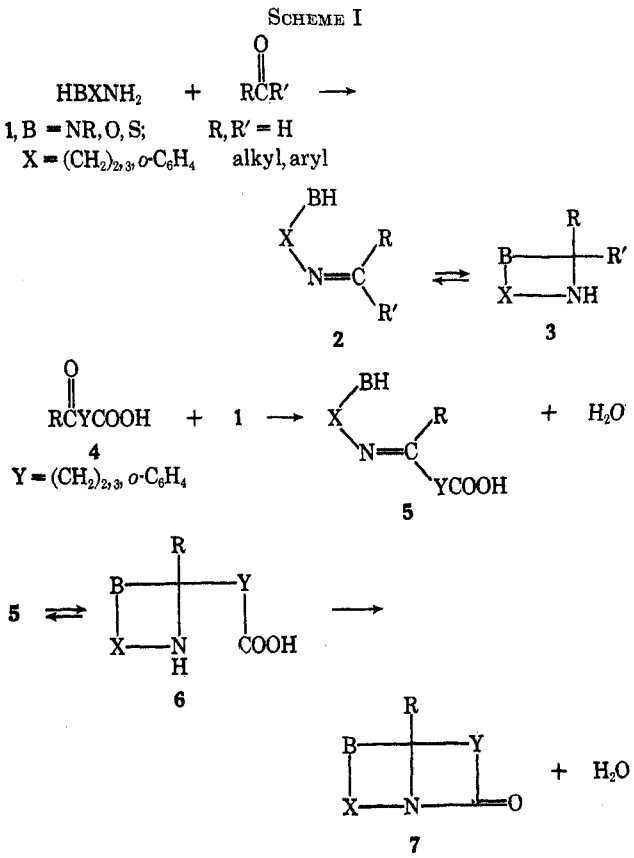
Received March 21, 1968

The condensation of a γ- or δ-keto acid with a 1,2-, 1,3-, or 1,4-amino alcohol, diamine, or mercaptoamine gave products containing lactams with an additional N-, O-, or S-containing ring fused on the a face of the lactam ring. The nuclear magnetic resonance of several ring systems gave an unusually low field proton signal that was assigned to the H_B proton of CH_AH_BNCO (21). The occurrence of this low-field proton was dependent on the ring size and heteroatom present in ring B of 21.

The reaction of a 1,2- or a 1,3-amino alcohol,[1a,b] diamine,[1c,d] or mercaptoamine[1e] (1) with an aldehyde or ketone has found general synthetic application in the preparation of heterocyclic systems 3.[1] The formation of 3 arises from the intermediate Schiff base 2 which in some systems exists in a ring-chain tautomeric equilibrium[2] with 3. An extension of this synthesis to an aldehyde or keto acid 4 suggests that the expected Schiff base 5 can first cyclize to the amino acid 6 and then proceed to form a second ring (7) from the available amino and carboxyl groups (Scheme I).

At the time our work was initiated no systematic study of the synthesis of compounds 7 by this reaction had been carried out. Limited studies of 2-mercaptoethylamine,[3a-d] cysteine,[3a] *o*-phenylenediamine,[3e-g] 2-aminobenzylamine,[3f] δ,δ′-diamino-*o*-xylene,[3e] 1,8-naphthalenediamine,[3e] and 2,2′-diaminobiphenyl[3e] with selected oxo acids (4) gave the heterocyclic systems 7 and their dehydrogenated[3e,g] analogs. Sulkowski[4] reported that aliphatic diamines and *o*-phenylenediamines react with 2-aroylbenzoic acids[4a] and 3-aroylpropionic acids[4b] to give medium-sized heterocycles 8. Geigy[5] workers carried out similar reactions with diamines, aminothiols, and amino alcohols and have assigned the fused-ring structure 9 to these condensation products. Very recently two papers[6a,b] and a patent[6c] appeared that presented evidence to show that the products from 2-aroylbenzoic acids and ethylenediamines are 5H-imidazo[2,1-*a*]isoindol-5-ones (9) and not 2,5-benzodiazocin-1-ones (8) as reported earlier.[4a]

SCHEME I



In the present paper we report our findings on the type of product formed when an amino alcohol, a diamine, or a mercaptoamine is condensed with 2-benzoylbenzoic, 3-benzoylpropionic, or 4-benzoylbutyric acids.

(1) For a general survey, see (a) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, John Wiley & Sons, Inc., New York, N. Y., 1957, pp 391–395; (b) N. H. Cromwell, ref 1a, Vol. 6, pp 541–544; (c) E. S. Schipper and A. R. Day, ref 1a, Vol. 5, p 245; (d) G. W. Kenner and Sir A. Todd, ref 1a, Vol. 6, pp 314–316; (e) J. M. Sprague and A. H. Land, ref 1a, Vol. 5, pp 697–702; (f) J. W. Keana, S. B. Keana, and D. Beetham, *J. Amer. Chem. Soc.*, **89**, 3055 (1967).

(2) For a discussion of this problem, see R. M. Srivastaba, K. Weissman, and L. B. Clapp, *J. Heterocycl. Chem.*, **4**, 114 (1967).

(3) (a) G. L. Oliver, J. R. Dann, and J. W. Gates, *J. Amer. Chem. Soc.*, **80**, 702 (1958); (b) D. Todd and S. Teick, *ibid.*, **75**, 1895 (1953); (c) R. G. Hiskey and S. J. Dominianni, *J. Org. Chem.*, **30**, 1506 (1965); (d) H. H. Wasserman, F. M. Precopio, and T. C. Liu, *J. Amer. Chem. Soc.*, **74**, 4093 (1952); (e) E. F. M. Stephenson, *J. Chem. Soc.*, 2354 (1954); (f) E. F. M. Stephenson, *ibid.*, 5024 (1952); (g) H. Hatt and E. F. Stephenson, *ibid.*, 199 (1952).

(4) (a) American Home Products Corp., Belgian Patent 646,221 (1965), and Netherlands Patent Application 6,403,794 (1965); *Chem. Abstr.*, **63**, 9972 (1965). (b) T. S. Sulkowski, U. S. Patent 3,293,243 (Dec 20, 1966); *Chem. Abstr.*, **66**, 4412 (1967).

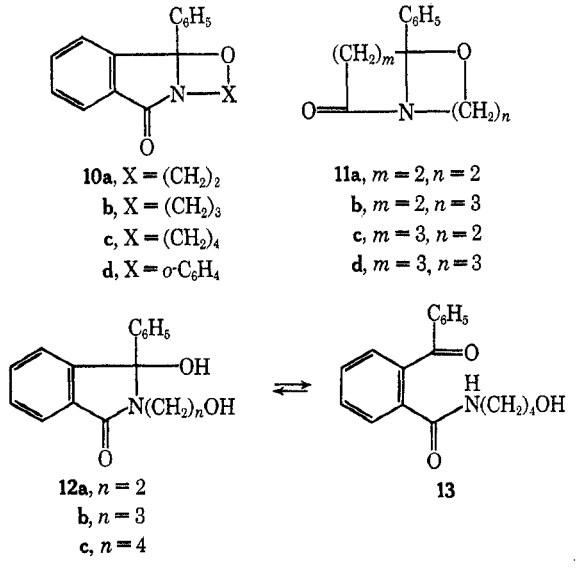
(5) J. R. Geigy, A.G. Belgian Patent 659,528 (Aug 10, 1965); *Chem. Abstr.*, **64**, 3545 (1966); Belgian Patent 659,530 (Aug 10, 1965); *Chem. Abstr.*, **64**, 6664 (1966), and Netherlands Patent Application 6,501,640 (Aug 12, 1965).

(6) (a) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967); (b) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967); (c) American Home Products Corp., Belgian Patent 679,508 (Oct 14, 1966).

The reaction of 2-benzoylbenzoic acid with ethanolamine gave a $C_{16}H_{13}NO_2$ compound that had a characteristic phthalimidine carbonyl band[7] at 5.85 μ and ultraviolet spectrum with strong end absorption in the 210–225-mμ region. These data are in agreement with the oxazolo[2,3-*a*]isoindol-5(9bH)-one structure **10a**. In a similar manner 3-aminopropanol and 4-aminobutanol were allowed to react with 2-benzoylbenzoic acid to give the homologous ring systems **10b** and **10c** and 2-aminophenol afforded the isoindolo[1,2-*b*]benzoxazol-6-one **10d**.

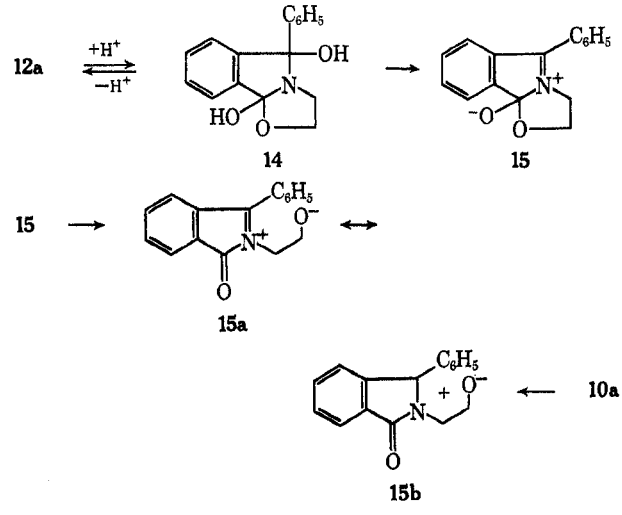
To obtain additional support for the structure of **10a–c** it was decided to prepare them from intermediates where the isoindolone ring was present before the additional alkylenoxy ring was formed. Reaction of 2-benzoylbenzoyl chloride with the above amino alcohols afforded the corresponding hydroxyalkylamines. The uv and ir data of the amides from ethanolamine and propanolamine were in agreement with assigning them as 3-phenylphthalimidines **12a–b**. The compound from 4-aminobutanol gave spectral data in agreement with the cyclic amide **12c** and in addition a weak band at 6.01 μ suggests that some of the tautomeric[8] benzoylamide **13** may be present (Scheme II).

SCHEME II



When a toluene solution of **12b** or **12c** was refluxed with a catalytic amount of acid they gave **10b** and **10c**. Treatment of **12a** in a similar manner did not give the expected **10a**. Instead, a polar compound, isomeric with **10a**, was obtained. The uv spectrum of this substance gave a maximum at 251 mμ and the nmr spectrum disclosed a CH_2CH_2 group and nine aromatic hydrogens, and an ir band at 5.83 μ suggested a C=N or C=O group.[9] The mass spectrum gave a parent peak at 251 ($C_{16}H_{13}NO_2$) and a fragmentation pattern that was indistinguishable from that given by **10a**. Based on these data we propose **15** as a structure for this compound. A possible pathway for forming **15** is the dehydration of the intermediate **14**. The identical mass spectrum given by **10a** and **15** must be due to the formation of a common molecular ion. Such an ion can readily be formed by breaking the C—O—C bond in **10a** and **15** to give the two canonical forms **15a** and **15b** (Scheme III).

SCHEME III



Additional support for structure **15** was obtained by lithium aluminum hydride reduction to 2-(2-hydroxyethyl)-1-phenylisoindoline. The latter structure was confirmed by nmr data and independently by its synthesis from 2-(2-hydroxyethyl)-3-phenylphthalimidine. When 3-benzoylpropionic or 4-benzoylbutyric acid was condensed with ethanolamine or 3-aminopropanol the fused lactones **11a–d** were obtained. Consistent with these structures the uv spectrum gave isolated phenyl absorption. Additional evidence for these structures was obtained by reduction of **11b** and **11c** to 1-(3-hydroxypropyl)-2-phenylpyrrolidine and 1-(2-hydroxyethyl)-2-phenylpiperidine.

The condensation of ethylenediamine with 2-benzoylbenzoic acid in refluxing toluene gave a novel compound. Comparison of the uv spectrum and the ir carbonyl frequency of this substance with that of the **10a** indicated that they both possessed similar skeletons, and that this compound is the 5H-imidazo[2,1-*a*]-isoindol-5-one[6a,b] (**16a**) rather than the benzophenonimine structure (**8**) reported[4a] earlier. The reaction of 3-*p*-chlorobenzoylpicolinic acid with ethylenediamine gave a product that had analytical and spectral properties in accord with the tricyclic structure **16e** and not the reported[4a] nine-membered ring (**8**).

When 2-benzoylbenzoic acid was allowed to react with 1,3-diaminopropane there was obtained a compound that gave spectral data (Table I) in agreement with the isoindolone structure **16c** rather than the reported[4a] nine-membered-ring system (**8**). A similar reaction between 2-benzoylbenzoic and 1,4-diaminobutane did not give the expected **16d** ($C_{18}H_{18}N_2O$) but instead a polar $C_{18}N_{20}N_2O_2$ compound that has been formulated as α-(4-aminobutylimino)-α-phenyl-*o*-toluic acid (**17b**).[10] The ir spectrum of **17b** gave broad

(7) (a) W. Flitsch, *Ann.*, **684**, 141 (1965); (b) M. V. Bhatt, *Tetrahedron*, **20**, 803 (1964); (c) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(8) For other examples of this type of tautomerism, see ref 7c.

(9) L. J. Bellamy, "Infrared Spectrum of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958.

(10) Sulkowski[6a] has reported that 2-*p*-chlorobenzoylbenzoic acid and 1.1 equiv of ethylenediamine in refluxing toluene gave the imine **17a** while with 3.0 equiv of ethylenediamine under the same conditions the cyclized system (**16b**) was obtained.

TABLE I

PHYSICAL AND SPECTRAL PROPERTIES AND ANALYSES

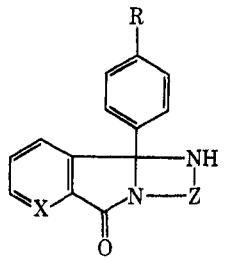
Compd no.	Yield, %	Bp (mm) or mp, °C (crystn solvent)[a]	Ir,[b] μ, band	Uv,[c] mμ (ε)	Empirical formula	Calcd, % C	H	N	O	Found, % C	H	N	O
10a	85	147–149 (A)	5.85 CO	225[d] (19,080)	$C_{16}H_{13}NO_2$[e]	76.5	5.2	5.6	12.7	76.6	5.4	5.8	12.6
10b	87	128–130 (A)	5.85 CO	219 (19,380) 255[d] (3,875)	$C_{17}H_{15}NO_2$	77.0	5.7	5.3	12.1	77.0	5.6	5.2	
10c	79	130–132 (A)	5.90 CO	216 (21,020) 251 (4,015)	$C_{18}H_{17}NO_2$	77.4	6.1	5.0	11.5	77.7	6.4	4.9	11.6
10d	37	135–138 (B)	5.78 CO	279 (24,500)	$C_{20}H_{13}NO_2$	80.3	4.3	4.7	10.7	80.3	4.3	4.7	10.8
11a	67	84.5–84.6 (C)	5.84 CO	251 (505) 259 (550) 267 (500)	$C_{12}H_{13}NO_2$	70.9	6.4	6.9	15.8	71.1	6.2	6.9	15.7
11b	74	77–79 (D)	5.91 CO	252 (475) 258 (525) 264 (495)	$C_{13}H_{15}NO_2$	71.9	7.0	6.5	14.7	71.8	7.0	6.5	15.0
11c	52	74–75 (E)	6.02 CO	251 (785) 257 (715) 263 (655)	$C_{13}H_{15}NO_2$	71.9	7.0	6.5	14.7	71.9	6.8	6.4	14.6
11d	45	72–73 (C)	6.10 CO	252 (655) 258 (695) 264 (660)	$C_{14}H_{17}NO_2$	72.9	7.4	6.1	13.8	72.5	7.5	6.2	13.8
16a	90	151–153[f] (F)	3.03 NH	225 (16,100)	$C_{16}H_{14}N_2O$[g]	76.8	5.6	11.2	6.4	76.6	5.8	11.3	6.7
16c	83	181–183 (A)	3.03 NH 5.93 CO	220 (19,860) 253 (3,505) 259 (3,505)	$C_{17}H_{16}N_2O$[h]	77.3	6.1	10.6	6.0	77.6	6.1	10.6	6.2
16d	75	180–182 (A)	3.00 NH 5.91 CO	259[d] (2,925)	$C_{18}H_{18}N_2O$[i]	77.7	6.5	10.1	5.7	77.6	6.8	10.3	6.0
16e	86	225–227 (F)	3.07 NH 5.85 CO	225 (15,860) 268 (4,955) 273 (4,975)	$C_{15}H_{12}ClN_3O$	62.9	4.3	14.8	5.6	62.8	4.1	14.6	
16f	66	158 (G)	3.01 NH 5.89 CO	250[d] (11,070) 305[d] (2,970)	$C_{20}H_{14}N_2O$	80.5	4.7	9.4	5.4	80.6	4.9	9.4	5.4
18a	71	129–130 (H)	3.04 NH 5.93 CO	212 (7,590) 246 (110) 251 (155) 257 (195) 263 (150)	$C_{12}H_{14}N_2O$	71.3	7.0	13.9	7.9	71.6	7.3	13.6	7.9
18b	66	132–132.5 (I)	3.04 NH 5.94 CO		$C_{13}H_{16}N_2O$	72.2	7.5	13.0	7.4	72.3	7.8		7.5
18c	45	132–133 (E)	3.07 NH 6.15 CO	247 (1,045) 251 (1,510) 257 (1,625) 267 (580)	$C_{13}H_{16}N_2O$	72.2	7.5	13.0	7.4	72.5	7.8	12.9	7.5
18d	42	140–141 (E)	3.05 NH 6.12 CO	212 (9,285) 251 (180) 257 (210) 263 (160)	$C_{14}H_{18}N_2O$	73.0	7.9	12.2	6.9	73.0	7.8	12.1	6.8
20a	68	103–104 (G)	5.83 CO	No max	$C_{16}H_{13}NOS$[j]	71.8	5.1	5.2	5.9	71.6	5.1	5.2	5.7
20b	70	156–159 (B)	5.84 CO	284[d] (1,780)	$C_{20}H_{13}NOS$	76.2	4.2	4.4	5.1	75.8	4.3		5.1
20c	67	105–106 (E)	6.08 CO	249 (645) 261 (665) 267 (535)	$C_{13}H_{15}NOS$	71.9	7.0	6.4	14.7	71.9	6.8	6.4	14.6
22a	60	124–126	3.01 NH 5.88 CO		$C_{11}H_{12}N_2O$	70.2	6.4	14.9	8.5	70.1	6.6	14.8	8.7
22b	85	165–168 (0.5)	3.02 NH 5.89 CO		$C_{12}H_{14}N_2O$	71.3	7.0	13.9	7.9	70.8	7.2	14.1	

[a] Recrystallization from the following solvents: A, methanol; B, chloroform–pentane–diethyl ether; C, pentane–diethyl either; D, diethyl ether; E, ethyl acetate; F, ethanol; G, ethanol-water; H, toluene; I, isopropyl alcohol. [b] The assignments are based on values reported in ref 7 and L. J. Bellamy, "The Infra-red Spectra of Complex Organic Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958. [c] All spectra were determined in 95% ethanol. [d] This is an inflection, not a maximum. [e] The mass spectrum exhibits a molecular ion peak at 251 ($C_{16}H_{13}NO_2$) with abundant fragment peaks at *m/e* 221 ($M^+ - 30$, CH_2O), 193 ($M^+ - 58$, OCH_2-CH_2N), 174 ($M^+ - 77$, C_6H_5), 165 ($M^+ - 86$; $CONCH_2CH_2O$), 147 ($M^+ - 104$, C_6H_4CO), 130, and 77 ($C_6H_5^+$). [f] Lit.[6b] mp 148–150°. [g] The mass spectrum exhibits a molecular ion peak at *m/e* 250 ($C_{16}H_{14}N_2O$) with abundant fragment peaks at *m/e* 221 ($M^+ - CH_2NH$), 220 ($M^+ - CH_4N$), 193 ($M^+ - NCH_2CH_2NH$), 173 ($M^+ - C_6H_5$), 130 ($M^+ - 85$, $CONCH_2CH_2NH$), 130 ($M^+ - 120$), and 77 ($C_6H_5^+$). [h] The mass spectrum exhibits a molecular ion peak at *m/e* 264 ($C_{17}H_{16}N_2O$) with abundant fragment peaks at *m/e* 235 ($M^+ - 29$, CH_2NH), 234 ($M^+ - 30$, CH_2NH_2), 206 ($M^+ - 58$, $CH_2CH_2NH_2$), 187 ($M^+ - 77$, C_6H_5), 179 ($M^+ - 85$), 165 ($M^+ - 99$), 159 ($M^+ - 105$), 130 ($M^+ - 134$), and 77 ($C_6H_5^+$). [i] The mass spectrum exhibits a molecular ion peak at 278 ($C_{18}H_{18}N_2O$) with abundant fragment peaks at *m/e* 221 ($M^+ - 57$, CH_2CH_2NH), 201 ($M^+ - 77$, C_6H_5), 166, 131, 112, and 77 ($C_6H_5^+$). [j] Lit.[3c] mp 104–106 and 109–110°.

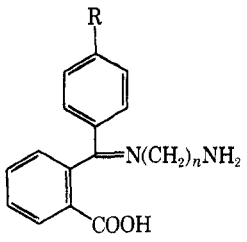
absorption at 3.1–3.4 and a strong band at 6.16 μ typical of a NH_3^+ and a CO_2^- grouping, respectively, while the uv spectrum gave a benzophenonimine maximum[11] at 240 mμ. When the reaction between 2-benzoylbenzoic acid and 1,4-diaminobutane was carried out in refluxing xylene a $C_{18}H_{18}H_2O$ compound was isolated. The spectral data (Table I) are in agreement with assigning this compound as the 7H-[1,3]diazepino-[2,1-*a*]isoindol-7-one (**16b**) rather than the reported[4a] ten-membered-ring system (**8**). The imine **17b**, a probable intermediate[12] in the direct formation of **16d**, could be converted into **16d** by removal of water in refluxing xylene.

From *o*-phenylenediamine and 2-benzoylbenzoic acid there was obtained a compound that had spectral and analytical properties (Table I) consistent with the 11H-isoindolo[2,1-*a*]benzimidazol-11-one (**16f**) rather than the reported[4a] medium-sized-ring system (**8**).

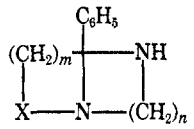
When 3-benzoylpropionic or 4-benzoylbutyric acid was allowed to react with ethylenediamine or 1,3-diaminopropane there was obtained fused lactam structures **18a–d**. We have ruled out the previously[4b] assigned eight- and nine-membered rings (**8**) for compounds **18a** and **18b** on the basis of the following data.



16a, R = H; X = CH; Z = $(CH_2)_2$
b, R = Cl; X = CH; Z = $(CH_2)_2$
c, R = H; X = CH; Z = $(CH_2)_3$
d, R = H; X = CH; Z = $(CH_2)_4$
e, R = Cl; X = N; Z = $(CH_2)_2$
f, R = H; X = CH; Z = *o*-C_6H_4



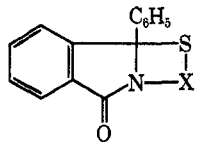
17a, n = 2; R = Cl
b, n = 4; R = H



18a and **b**, m = 2; n = 2, 3; X = CO
c and **d**, m = 3; n = 2, 3; X = CO
19a and **b**, m = 2; n = 2, 3; X = CH_2
c and **d**, m = 3; n = 2, 3; X = CH_2

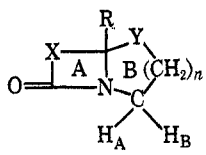
The uv spectrum of all four lactam systems gave isolated phenyl absorption rather than the phenylimine system present in **8**. The ir spectrum of **18a** and **18b** gave five-membered lactam carbonyl bands while **18c** and **18d** afforded characteristic six-membered lactam carbonyl bands. Treatment of **18a–d** with lithium aluminum hydride in refluxing diethyl ether gave the corresponding reduced systems **19a–d**. The presence of one D_2O exchangeable proton in the nmr spectra of these compounds supported the NH group.

The reaction of 2-mercaptoethylamine with 4-benzoylbutyric acid has been repeated. Our findings (Table I) are in agreement with that of Hiskey[3c] in assigning the product from this reaction as 8a-phenylhexahydro-5H-thiazolo[3,2-*a*]pyridin-5-one (**20c**). In addition we have condensed 2-benzoylbenzoic acid with 2-mercaptoethylamine and 2-aminothiophenol to obtain the thiazolo[2,3-*a*]isoindol-5(9bH)-one **20a** and the isoindolo[1,2-*b*]benzothiazol-11-one **20b**.

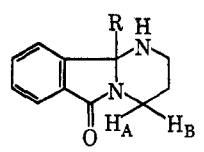


20a, X = $(CH_2)_2$
b, X = *o*-C_6H_4

The nmr spectral data on the ring systems described above are listed in Table II according to the order of increase in the size of ring B in the generalized structure **21**. Several compounds gave an unusually low-field proton signal in the 4.22–4.75-ppm range (H_B in Table II). The presence of this signal was dependent on (1) the size of ring B, (2) the type of heteroatom Y, and independent of the size of ring A. When Y is N, H_B appears as a complex doublet only when ring B is six or seven membered (compare **16a**, **16e**, and **18a,c** with **16c,d**, **18b,d**, and **22a,b**). In the O analogs H_B appears as a complex doublet when ring B contains five, six, or seven members and X is an *o*-phenylene (**10a,b,c**) but is present only in the six-membered compounds when X is alkylene (compare **11a,c** with **11d**). When X is S, H_B occurs as a complex multiplet and is present when ring B contains five or six members (**20a,c**).



21
n = 1, 2, 3; Y = NH, O, S
R = H, CH_3, C_6H_5
X = $(CH_2)_{2,3}$, *o*-C_6H_4



22a, R = H
b, R = CH_3

Hiskey[3c] has also reported that **20c** gave a low-field proton that was located on the carbon atom attached to the lactam nitrogen (CH_AH_B in ring B of **21**). The cause of this shift was attributed to the "bent geometry" of the ring system.

Models of the ring systems that displayed the low-field proton suggested that the shift could be caused by the deshielding[13] influence of either the phenyl or

(11) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954.

(12) The imine **17b** represents an example of the general formula **5** that was postulated as the first intermediate in the condensation of $BHXNH_2$ (**1**) with keto acids.

(13) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chapter 7.

TABLE II

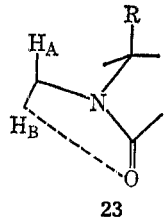
PROTON MAGNETIC RESONANCE DATA[a]

Compd no.	Ring type[b] A	B	X	Y	Proton assignments,[c] ppm H_B[d]	NH[e]	Aliphatic protons[f]
16a	5	5	*o*-C_6H_4	NH		2.21	3.17 (2 H, m, CH_2N), 3.68 (2 H, m, CH_2NCO)
16e	5	5	*o*-C_5H_3N	NH		3.61	3.12 (2 H, m, CH_2N), 3.61 (2 H, m, CH_2NCO)
18a	5	5	$(CH_2)_2$	NH		2.08	2.13–3.90 (8 H, m)
10a	5	5	*o*-C_6H_4	O	4.22 m		3.30 (1 H, m, CH_AN), 4.22 (2 H, m, CH_2O)
11a	5	5	$(CH_2)_2$	O			2.41 (5 H, m), 3.62 (3 H, m)
20a	5	5	*o*-C_6H_4	S	4.45 m		3.33 (3 H, m, CH_ACH_2)
18c	6	5	$(CH_2)_3$	NH		2.28	1.66 (3 H, m), 2.42 (4 H, m), 3.17 (2 H, m), 3.72 (1 H, m)
11c	6	5	$(CH_2)_3$	O			1.97 (6 H, m), 3.33 (2 H, m), 3.96 (2 H, m)
20c	6	5	$(CH_2)_3$	S	4.45 m		1.68 (2 H, m, CCH_2C), 2.68 (6 H, m), 3.64 (1 H, CH_AN)
22a	5	6[g]	*o*-C_6H_4	NH	4.48 d, J = 13.0	1.65	1.62 (2 H, m, CCH_2C), 3.21 (3 H, m, NCH_2 and NCH_A), 5.18 (1 H, s, ArCHN)
22b	5	6[h]	*o*-C_6H_4	NH	4.48 d, J = 13.0	1.71	1.65 (3 H, s, CH_3), 1.60 (2 H, m, CCH_2C), 3.22 (3 H, m, NCH_2 and NCH_A)
16c	5	6	*o*-C_6H_4	NH	4.50 d, J = 13.0	2.10	1.50 (2 H, m, CCH_2C), 3.01 (3 H, m, NCH_2 and NCH_A)
18b	5	6	$(CH_2)_2$	NH	4.27 d, J = 13.0	1.75	1.48 (2 H, m), 1.70 (5 H, m)
10b	5	6	*o*-C_6H_4	O	4.48 d, J = 13.0		1.68 (2 H, m), 3.08 (1 H, m), 3.89 (2 H, m)
11b	5	6	$(CH_2)_2$	O	4.28 d, J = 13.0		2.17 (7 H, m), 3.75 (2 H, m)
18d	6	6	$(CH_2)_3$	NH	4.75 d, J = 13.0	1.78	1.72 (6 H, m), 2.63 (5 H, m)
11d	6	6	$(CH_2)_3$	O	4.72 d, J = 13.0		2.08 (9 H, m), 3.72 (2 H, m, CH_2O)
16d	5	7	*o*-C_6H_4	NH	4.28 d, J = 13.0	1.92	1.82 (5 H, m), 2.85 (2 H, m)
10c	5	7	*o*-C_6H_4	O	4.15 d, J = 13.0		1.73 (4 H, m, CCH_2CH_2C), 3.25 (3 H, m, OCH_2 and NCH_A)

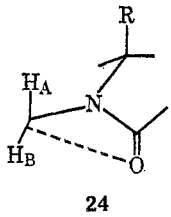
[a] The spectra were obtained as $CDCl_3$ solutions on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal $SiMe_4$ standard. The J values are in cycles per second. [b] The definitions of A, B, X, and Y refer to structure **21**. Unless indicated otherwise R in **21** is a C_6H_5 group. [c] The aromatic protons for the compounds in this table were located in the δ 7.00–7.90 region. [d] This is H_B in **21**. [e] All NH groups were confirmed by D_2O exchange at room temperature. [f] In several compounds the aliphatic protons were present as a series of overlapping multiplets. The value in the tables refers to the center of these overlapping multiplets. [g] R in **21** is H. [h] R in **21** is CH_3.

carbonyl group. To distinguish this influence compounds **22a** and **22b** (Table II) were prepared from 1,3-propanediamine and the appropriate acylbenzoic acid. In both cases a low-field proton was observed, thereby ruling out the deshielding influence of the phenyl group.

Studies on the anisotropic[14] effect of the carbonyl[15] group have shown that this group exerts maximum deshielding effect on a hydrogen atom when the oxygen and hydrogen atoms lie in the same plane. Inspection of the CH_AH_BNCO region in the heterocyclic systems represented by **21** revealed that when ring B is six or seven membered the preferred conformational orientation of the equatorial proton H_B is such that it lies in the same plane as the lactam oxygen atom (**23**). When ring B is five membered the orientation of H_B is that where the carbonyl oxygen lies approximately in the plane of the carbon atom or about equidistant from H_A and H_B (**24**). Model **23** clearly indicates



23



24

why a low-field proton exists in all cases where ring B is six or seven membered. When ring B is five membered the situation is not so clear since compounds **10a**, **20a**, and **20c** possess a low-field proton even though model **24** does not predict this. The presence of the low-field proton in these systems indicates that the conformational orientation is not readily predicted from inspection of simple molecular models. The orientation of the CH_AH_B region in these compounds is undoubtedly one where the H_B proton lies in the plane of the carbonyl group owing to a stretching or bending[3c] of the O or S atoms in ring B.

The deshielding influence of the carbonyl group in some lactam systems related to those prepared in this work has also been reported.[16–18]

Experimental Section[19]

General Procedure for the Condensation of Keto Acids with Amines.—The appropriate amino alcohol, aminothiol, or diamine (0.20 mol), keto acid (0.10 mol), solvent (toluene or xylene), and a catalytic amount of acid (0.5 g) was placed in a flask equipped with a stirrer and a Dean–Stark tube. The mixture was stirred and refluxed until the level of the "water layer" (mixture of water and amine) in the side arm remains constant (5–24 hr). The reaction was allowed to cool to room temperature and the resultant solid was removed by filtration. If a solid was not obtained on cooling the solvent was removed *in vacuo* and the resultant residue was either distilled or crystallized from an appropriate solvent. The compounds prepared by this procedure are listed in Table I.

Reaction of 2-Benzoylbenzoic Acid Chloride with Amino Alcohols 11a–c.—A mixture of acid chloride (0.10 mol) and amino alcohol (0.20 mol, **11a–c**) in 125 ml of anhydrous dimethyl-

(14) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1966, p 24; H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967).

(15) For some critical comments on the accepted model for the carbonyl group, see G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenohlio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(16) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965).

(17) J. S. Fitzgerald, S. R. Johnson, J. A. Lamberton, and A. H. Redcliffe, *Aust. J. Chem.*, **19**, 151 (1966).

(18) M. Visconti and W. Kaiser, *Helv. Chim. Acta*, **48**, 127 (1965).

(19) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal $SiMe_4$ standard. Infrared spectra were determined as KBr pellets using a Perkin-Elmer Infracord. Ultraviolet spectrum were carried out on a Beckman Model DB or a Cary Model 15 spectrometer. Mass spectra were determined on a Consolidated Electronics Co. mass spectrometer Model 21-103 C, equipped with an all-glass heated inlet.

formamide was maintained at 60° for 48 hr. The solvent was removed *in vacuo* and the residue crystallized from the appropriate solvent.

2-(2-Hydroxyethyl)-3-hydroxy-3-phenylphthalimidine (**12a**, 87%) had mp 124–126° (CH_3OH–H_2O); ir (KBr) 2.97 and 3.12 (OH), 5.92 μ (C=O), uv max (C_2H_5OH) 252 mμ (ε 3200), 264 (2495), 285 (shoulder, 780). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.7; N, 5.2; O, 17.1. Found: C, 71.4; H, 5.6; N, 5.2; O, 17.8.

2-(3-Hydroxypropyl)-3-hydroxy-3-phenylphthalimidine (**12b**, 94%) had mp 115–117° (CH_3OH); ir (KBr) 3.0–3.2 (OH), 5.92 μ (C=O); uv max (C_2H_5OH) 253 mμ (ε 2450), 265 (2800). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.0; N, 4.9; O, 16.9. Found: C, 72.0; H, 6.2; N, 5.0; O, 16.9.

2-(4-Hydroxybutyl)-3-hydroxy-3-phenylphthalimidine (**12c**, 97%) had mp 150–152° (CH_3OH); ir (KBr) 3.020–3.08 (OH), 5.95 (C=O, lactam), 6.02 μ (C=O); uv max (C_2H_5OH) 252 mμ (ε 4465), 263 (3230). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4; N, 4.7; O, 16.1. Found: C, 73.0; H, 6.6; N, 4.7; O, 16.3.

Cyclization of 12b,c to 10b,c.—A mixture of **12b** or **12c** (10 or 5 g), *p*-tolSO_3H (0.5 or 0.3 g) and toluene (150 or 75 ml) were refluxed (20 hr). Crystallization of both products from CH_3OH gave, respectively, 8.2 g (87%) of **10b**, mp 127–128°, and 3.8 g (80%) of **10c**, mp 132–133°. Comparison of the ir and uv spectra and mixture melting points of **10b** and **10c** prepared above showed them to be identical.

Cyclization of 2-(2-Hydroxyethyl)-3-hydroxy-3-phenylphthalimidine (12a) to 5-Phenyl-2,3-dihydro-5H-oxazolo[2,3-*a*]isoindolium 5-Oxide (15).—A mixture of 10.0 g of **12a**, 0.5 g of *p*-tolSO_3H and 150 ml of toluene was stirred and refluxed for 18 hr in a flask equipped with a Dean–Stark tube. The solvent was removed *in vacuo* to give 9.4 g (98%) of **15**: mp 243–245°; ir (KBr) 5.83, 6.93, 7.22, 7.71, 9.14, 9.26, 9.64 and 11.90 μ, (CH_2Cl_2) 5.86, (CS_2) 5.88; uv max (CH_3CN) 251 mμ (ε 4065); nmr ($CDCl_3$) δ 2.68 (2 H, m), 3.81 (1 H, m), 4.26 (1 H, m) 7.05–7.60 (8 H, m) and 7.92 (1 H, m); tlc on silica gel gave R_f 0.06 (CH_2Cl_2), 0.10 ($CHCl_3$), 0.73 (acetone). The mass spectrum of **15** was indistinguishable from **10a**'s and exhibited a molecular ion peak at 251 ($C_{16}H_{13}NO_3$) with abundant fragment peaks at *m/e* 221 ($M^+ - 30$, CH_2O), 193 ($M^+ - 58$, OCH_2CH_2N), 174 ($M^+ - 77$, C_6H_5), 165 ($M^+ - 86$, $CONCH_2CH_2O$), 147 ($M^+ - 104$, C_6H_4CO), 130, and 77 ($C_6H_5^+$). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6; O, 12.7. Found: C, 76.2; H, 5.2; N, 5.5; O, 12.5.

Lithium Aluminum Hydride ($LiAlH_4$) Reduction of 15 to 2-Hydroxyethyl-1-phenylisoindoline.—To a stirred suspension of 1.9 g (0.05 mol) of $LiAlH_4$ in 100 ml of diethyl ether (nitrogen atmosphere) was added dropwise 5.0 g (0.02 mol) of **15** in 75 ml of diethyl ether. The mixture was stirred and refluxed for 26 hr, cooled in an ice bath and treated with 3.8 ml of 2 *N* sodium hydroxide and 5.7 ml of water. The salts were filtered off and the filtrate was concentrated. The residue was distilled in a kugelrohr at 180° (0.5 mm) to give 3.9 g (81%) of title compound as a viscous oil: ir ($CHCl_3$) 2.92 μ (OH); nmr ($CDCl_3$) δ 2.85 (2 H, m, CH_2N), 3.12 (s, D_2O exchangeable, OH), 3.58 (2 H, m, CH_2O) 3.78 (H_A), 4.52 (H_B), 4.79 (H_C, J_{AB} = 12 cps, J_{AC} = 3 cps, J_{BC} = 2 cps, $ArCH_AH_BNCH_CAr$). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.3; H, 7.2; N, 5.9. Found: C, 80.2; H, 7.2; N, 5.7.

2-Hydroxyethyl-3-phenylphthalimidine.—A mixture of 75 g (0.33 mol) of 2-benzoylbenzoic acid, 30 g (0.50 mol) of ethanolamine, 15 g of Raney nickel no. 28, and 500 ml of isopropyl alcohol was hydrogenated at 100° (1500-psi initial pressure) to give 26.4 g of the title compound: mp 110–112° (CH_3OH–H_2O); ir (KBr) 2.97 (OH), 5.76 μ (C=O); nmr ($CDCl_3$) δ 3.78 (1 H, D_2O exchangeable, OH) 3.13 (H_A), 3.72 (2 H_C), 4.00 (H_B, ABC multiplet, $NCH_AH_BCH_CO$), 5.61 (1 H, s, CH), and 7.9–7.9 (m, nine aromatic H). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 5.9; N, 5.5; O, 12.7. Found: C, 75.6; H, 5.8; O, 12.5. Reduction of 2-hydroxyethyl-1-phenylphthalimidine with $LiAlH_4$ as described above gave 2-hydroxyethyl-1-phenylisoindoline (76%).

1-(3-Hydroxypropyl)-2-phenylpyrrolidine from 11b.—The $LiAlH_4$ procedure described above was used. There was obtained the title compound (87%): mp 49–50° (diethyl ether–pentane); ir (CH_2Cl_2) 2.87 μ (OH); nmr ($CDCl_3$) δ 1.17–3.82 (13 H, very complex series signals, aliphatic H), 4.73 (OH, D_2O exchangeable), and 7.30 (5 H, s, C_6H_5). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 75.8; H, 9.2; N, 7.0.

A mixture of 2.9 g (0.02 mol) of 2-phenylpyrrolidine,[20] 1.4 g (0.01 mol) of 3-bromopropanol, and 15 ml of anhydrous toluene was stirred and refluxed for 56 hr. The mixture was washed twice with water, dried ($MgSO_4$), filtered, and then concentrated. Distillation gave 0.9 g of 1-(3-hydroxypropyl)-2-phenylpyrrolidine, bp 115–117° (1.0 mm), mp 48–50°.

1-(2-Hydroxyethyl)-2-phenylpiperidine from 11c.—The $LiAlH_4$ procedure described above was used. There was obtained the title compound (64%): bp 125–128° (1.0 mm); mp 57–59°; ir (CH_2Cl_2) 2.79 μ (OH); nmr ($CDCl_3$) δ 1.32–3.88 (13 H, complex overlapping signals, aliphatic H), 1.65 (OH, D_2 exchangeable), and 7.28 (5 H, s, C_6H_5). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; O, 7.8. Found: C, 75.9; H, 9.1; O, 7.6. A mixture of 3.2 g (0.02 mol) of 2-phenylpiperidine,[21] 1.3 g (0.01 mol) of 2-bromoethanol, and 25 ml of anhydrous toluene was refluxed for 45 hr. The mixture was washed twice with water, dried ($MgSO_4$), filtered, and concentrated. The residue was distilled to give 0.9 g of 1-(2-hydroxyethyl)-2-phenylpiperidine, bp 122–124° (1.0 mm), mp 56–58°.

N-(4-Aminobutyl)-2-carboxybenzophenonimine (17b).—From 11.3 g (0.05 mol) of 2-benzoylbenzoic acid, 5.0 g (0.055 mol) of 1,4-diaminobutane, 0.6 g of *p*-tol-SO_3H, and 150 ml of toluene there was obtained 9.0 g of **17b**: mp 204–206° (methanol); ir (KBr) 2.92 (NH_3^+), 6.16 μ (CO_2^-); uv max (C_2H_5OH) 240 mμ (ε 12,380). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.9; H, 7.0; N, 9.4; O, 10.7. Found: C, 72.9; H, 7.0; N, 9.2; O, 11.2. When 7.4 g of **22c**, 0.3 g of *p*-tol-SO_3H, and 250 ml of xylene were refluxed for 12 hr there was obtained 5.9 g (83%) of **21d**, mp 180–182° (CH_3OH).

$LiAlH_4$ Reduction of 18a–d to 19a–d.—The $LiAlH_4$ procedure described above was followed. Compound **19a** (95%) had bp 100° (1.0 mm, kugelrohr); ir ($CHCl_3$) 2.98 μ (NH); nmr ($CDCl_3$) δ 1.81 (m, 4 H), 2.05 (1 H, D_2O exchangeable, NH), 2.92 (m, 6 H), 7.22, (m, 3 H, ArH), and 7.62 (m, 2 H, ArH). *Anal.* Calcd for $C_{12}H_{16}N_2$: C, 76.6; H, 8.5; N, 14.9. Found: C, 76.4; H, 8.3; N, 14.6.

Compound **19b** (94%) had bp 115° (0.5 mm, kugelrohr); $n^{20}D$ 1.5619; ir (CH_2Cl_2) 2.97 μ (NH); nmr ($CDCl_3$) δ 0.83 (1 H, m), 1.49–2.21 (5 H, m), 1.63 (NH, D_2O exchangeable), 2.60–3.49 (6 H, m), 7.28 (3 H, m, ArH), and 7.62 (2 H, m, ArH). *Anal.* Calcd for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0; N, 13.9. Found: C, 77.5; H, 9.2; N, 13.8.

Compound **19c** (97%) had mp 69–70° (C_5H_{12}); ir (CH_2Cl_2) 2.97 μ; nmr ($CDCl_3$) δ 1.17–2.05 (m, 6 H), 2.18 (s, 1 H, D_2O exchangeable, NH), 2.38–3.32 (m, 6 H), 7.20 (m, 3 H, ArH), and 7.63 (m, 2 H, ArH). *Anal.* Calcd for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0; N, 13.9. Found: C, 77.4; H, 9.2; N, 14.2.

Compound **19d** (95%) had bp 100° (0.7 mm, kugelrohr); ir (CH_2Cl_2) 2.95 μ (NH); nmr ($CDCl_3$) δ 0.78 (m, 1 H), 1.52 (s, 1 H, D_2O exchangeable, NH), 1.30–2.28 (m, 7 HO, 2.50–3.57), (m, 6 H), 7.32 (m, 3 H, ArH), and 7.65 (m, 2 H, ArH). *Anal.* Calcd for $C_{14}H_{20}N_2$: C, 77.7; H, 9.4. Found: C, 77.5; H, 9.2.

Registry No.—**10a**, 17494-19-8; **10b**, 17254-88-5; **10c**, 17254-91-0; **10d**, 16147-62-9; **11a**, 7088-08-6; **11b**, 7088-15-5; **11c**, 7088-09-7; **11d**, 7088-10-0; **12a**, 17254-83-0; **12b**, 17254-87-4; **12c**, 17254-90-9; **15**, 18409-52-4; **16a**, 5810-66-2; **16c**, 5983-52-8; **16d**, 5983-66-4; **16e**, 5983-70-0; **16f**, 16147-55-0; **17b**, 17254-96-5; **18a**, 7421-62-7; **18b**, 6029-25-0; **18c**, 6029-37-4; **18d**, 6029-43-2; **19a**, 18409-71-7; **19b**, 18409-72-8; **19c**, 18409-73-9; **19d**, 18409-74-0; **20a**, 5218-08-6; **20b**, 16147-71-0; **20c**, 2952-86-5; **22a**, 18440-63-6; **22b**, 6166-34-3; 2-hydroxyethyl-1-phenylisoindoline, 18409-76-2; 2-hydroxyethyl-3-phenylphthalimidine, 18409-77-3; 1-(3-hydroxypropyl)-2-phenylpyrrolidine, 18409-78-4; 1-(2-hydroxyethyl)-2-phenylpiperidine, 18409-79-5; **17b**, 17254-96-5.

Acknowledgment.—The authors express their appreciation to Mr. Urs Stoeckli and his associates for analytical and spectra data.

(20) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1281 (1958).
(21) C. G. Overberger and L. P. Herin, *ibid.*, **27**, 417 (1962).