To this mixture was added 0.67 g (2.0 mmol) of bromotriphenylmethane, and the contents were stirred at room temperature for 3 hr. The mixture was diluted with water and extracted with chloroform. The extracts were dried (Na₂SO₄), concentrated, and recrystallized from methanol to give 0.12 g (20%) of 9-triphenylmethyl-9H-purine-6(1H)-thione (X), mp 213–216°. The mass spectrum showed M⁺ at *m/e* 394.1292 (Calcd for C₂₄H₁₈N₄S: 394.1252). The analytical sample prepared by further recrystallization from methanol. *Anal.* Calcd for C₂₄H₁₈N₄S·0.25H₂O: C, 72.24; H, 4.67; N, 14.04; S, 8.04. Found: C, 72.11; H, 4.59; N, 13.97; S, 7.95.

Removal of the Triphenylmethyl Group from 9-Triphenylmethyl-9H-purine-6(1H)-thione (X).—A mixture of 0.0103 g (0.02 mmol) of X in 0.5 ml of 50% aqueous acetic acid was heated on a steam bath for 5 min. The cooled mixture was filtered to give 0.0061 g (90%) of triphenylcarbinol, mp 165–166°. The filtrate was concentrated by freeze-drying to give a yellow solid. Recrystallization from water gave 0.0044 g (98%) of purine-6(1H)-thione monohydrate, mp 308–312° dec (lit.¹⁵ mp 313–314°). The infrared spectrum of this sample was identical with the spectrum of an authentic sample.

Preparation of 9-Triphenylmethyl-6-benzylthiopurine (VIIIe) from 6-Benzylthiopurine.—The alkylation of 6-benzylthiopurine with bromotriphenylmethane under conditions similar to those used for the preparation of VIIIa gave a 60% yield of VIIIe,

(15) See Table II, footnote *i*.

mp 248–249°. The analytical sample prepared by further recrystallization from a N,N-dimethylformamide and methanol mixture had mp 249–250°. *Anal.* Calcd for C₃₁H₂₄N₄S: C, 76.83; H, 4.99; N, 11.56; S, 6.62. Found: C, 76.71; H, 5.12; N, 11.59; S, 6.56.

Preparation of 9-Triphenylmethyl-6-benzylthiopurine (VIIIe) from 9-Triphenylmethyl-9H-purine-6(1H)-thione (X).—A mixture of 0.085 g (0.218 mmol) of X, 0.02 g (0.218 mmol) of an anhydrous potassium carbonate, and 0.0373 g (0.218 mmol) of α-bromotoluene was stirred for 16 hr at 25°. The mixture was diluted with cold water and filtered. The precipitate was washed with ethanol and recrystallized from a N,N-dimethylformamide–methanol mixture to give 0.062 g (62%) of X, mp 248–251°. The ir spectra of this product was identical with VIIIe obtained by the alkylation of 6-benzylthiopurine with bromotriphenylmethane.

# Intramolecular Amidoalkylations at Carbon. Synthesis of Heterocyclic Amines

M. WINN AND H. E. ZAUGG

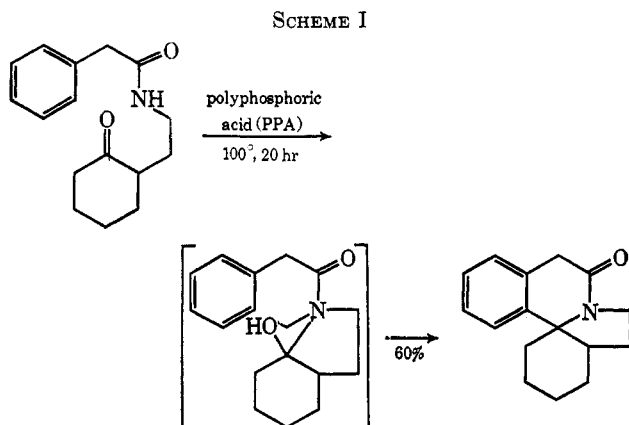*Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois 60064*

Received April 11, 1968

Amides of levulinic, 3-benzoylpropionic, *o*-benzoylbenzoic and phthalaldehydic acids with arylethylamines and benzylamines underwent double cyclization in strong acids, forming benzo-, dibenzo-, and thienoindolizines, and dibenzopyrrolizidines. Quaternary salts of benzoindolizines cleaved with lithium to give benzazonines.

The Friedel–Crafts-type reaction of α-amido alcohols with aromatic rings has been extensively reviewed.¹ However, only a few examples of cyclizations using this method have been reported.

$$-\text{C}-\text{N}-\text{C}-\text{OH} + \text{H}-\text{Ar} \xrightarrow{\text{H}^+} -\text{C}-\text{N}-\text{C}-\text{Ar} + \text{H}_2\text{O}$$
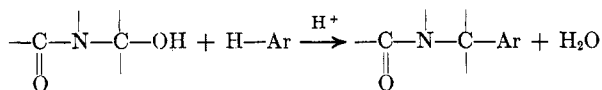
The first example of such a cyclization was reported by Belleau² in his synthesis of erythrina-like alkaloids (Scheme I). Mondon³ synthesized the same ring system in a slightly different manner, using the dehydrated keto amide as an intermediate. These workers were able to prepare methoxy derivatives using milder conditions. With dimethoxyphenyl and indole derivatives, Boekelheide⁴ and Winterfeldt⁵ found that dilute hydrogen chloride in alcohol sufficed to give excellent yields of cyclized products. Recently, Brown⁶ cyclized derivatives of isoquinolone to tetracyclic amides. After this work was completed, Wawzonek⁷ reported intramolecular amidoalkylations of indole derivatives.

SCHEME I

$n = 0, 1$

$R = CH_3, C_6H_5$

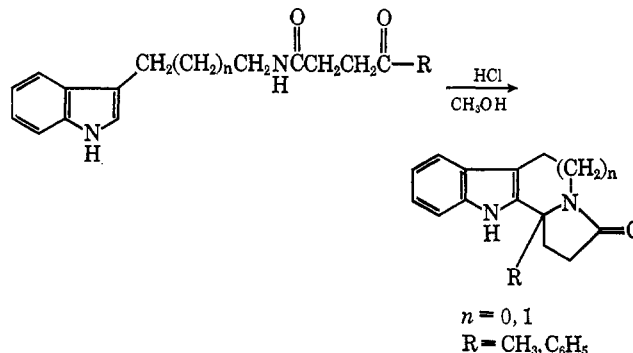These cyclizations are similar to our work except that we alkylated benzene and thiophene nuclei in-

(1) H. E. Zaugg and W. B. Martin, "Organic Reactions," Vol. 14, John Wiley and Sons, Inc., New York, N. Y., 1965, pp 52–270.

(2) B. Belleau, *J. Amer. Chem. Soc.*, **75**, 5765 (1953); *Can. J. Chem.*, **35**, 651, 663 (1967).

(3) A. Mondon, *Chem. Ber.*, **92**, 1461, 1472, 2543 (1959).

(4) V. Boekelheide, M. Muller, J. Jack, and T. Grossnickle, *J. Amer. Chem. Soc.*, **81**, 3955 (1959).

(5) E. Winterfeldt, *Chem. Ber.*, **97**, 2463 (1964).

(6) D. W. Brown and S. F. Dyke, *Tetrahedron*, **22**, 2429 (1966).

(7) S. Wawzonek and M. M. Maynard, *J. Org. Chem.*, **32**, 3618 (1967).

TABLE I

3-Hydroxyphthalimidines

No.	R	Mp, °C	Yield, %	Formula	Anal., %					
					Calcd (C)	Found (C)	Calcd (H)	Found (H)	Calcd (N)	Found (N)
1a	C_6H_5	151–152	68	$C_{21}H_{17}NO_2{}^a$	79.98	79.93	5.43	5.28	4.44	4.50
1b	$C_6H_3(OCH_3)_2$-3,4	85–90	66	$C_{23}H_{21}NO_4$	b					
1c	$C_6H_3(OCH_2O)$-3,4	170–172	71	$C_{22}H_{17}NO_4$	73.53	73.46	4.77	4.65	3.90	3.77
1d	$CH_2C_6H_5$	189–191	88	$C_{22}H_{19}NO_2$	80.22	80.14	5.81	5.78	4.25	4.01
1e	$CH_2CH_2C_6H_5$	129–131	58	$C_{23}H_{21}NO_2$	80.44	80.10	6.16	6.25	4.08	3.96
1f	$CH_2C_6H_3(OCH_3)_2$-3,4	150–152	33^c	$C_{24}H_{23}NO_4$	74.02	74.09	5.95	5.87	3.60	3.43
1g	$CH=CH_2$	145–147^d	66	$C_{17}H_{15}NO_2$						
2a	C_6H_5	137–139^e	45	$C_{15}H_{13}NO_2{}^f$						
2b	$CH_2C_6H_5$	153–154	50	$C_{16}H_{15}NO_2$	75.87	75.76	5.97	5.83	5.53	5.39

^{a} Nmr (CDCl$_3$), δ 4.04 (d, 1, J = 13 Hz), 4.14 (s, 1, OH), 4.52 (d, 1, J = 13), and 7.0–7.9 ppm (m, 14). Nmr of 1b–f are similar. ^{b} Contained chloroform of crystallization. ^{c} Prepared by refluxing amine and acid in pyridine overnight. ^{d} Mp 145–147°: P. Truitt, L. Brammer, and L. Creagh, *J. Med. Chem.*, **8**, 735 (1965). ^{e} Mp 143°: A. Dunet and A. Willemart, *Bull. Soc. Chim. Fr.*, 1045 (1948). ^{f} Nmr (CDCl$_3$), δ 4.15 (d, 1, J = 13), 4.50 (d, 1, J = 8, OH), 4.75 (d, 1, J = 8), 5.53 (d, 1, J = 8), and 7.2–7.7 ppm (m, 9). Nmr of 2b is similar.

TABLE II

ISOINDOLO[1,2-a]ISOQUINOLINES AND ISOINDOLO[1,2-a]ISOINDOLES

No.	R	Mp, °C	Yield, %	Reacn conditions^a	Formula	Anal., %					
						Calcd (C)	Found (C)	Calcd (H)	Found (H)	Calcd (N)	Found (N)
3a	H	173–175	65	A, 20°, 2 hr	$C_{22}H_{17}NO^b$	84.86	84.67	5.50	5.61	4.50	4.63
3b	OCH$_3$	201–202	91	B, 50°, 2 hr	$C_{24}H_{21}NO_3$	77.61	76.94	5.70	5.75	3.77	3.72
4a	H	210–211	75	C, 135°, 4 hr	$C_{21}H_{15}NO^c$	84.82	84.88	5.08	4.96	4.71	4.70
4b	OCH$_3$	212–213	64	D, 30°, 4 hr	$C_{23}H_{19}NO_3$	77.29	77.02	5.36	5.09	3.92	4.00
4c	OCH$_2$O	194–196	37	D, 30°, 3.5 hr	$C_{22}H_{15}NO_3$	77.41	76.26	4.43	4.52	4.10	4.00
5		114–116	84	A, 25°, 2 hr	$C_{16}H_{13}NO^d$	81.86	81.73	5.57	5.72	5.95	5.89

^{a} A, concentrated H$_2$SO$_4$; B, POCl$_3$; C, polyphosphoric acid; D, a mixture of 7:1 polyphosphoric acid–85% phosphoric acid, by volume. ^{b} Nmr (CDCl$_3$), δ 2.5–3.6 (m, 3), 4.16 (m, 1), 6.9–8.0 ppm (m, 13). ^{c} Nmr (CDCl$_3$), δ 4.33 (d, 1, J = 13), 5.16 (d, 1, J = 13), 7.2–8.0 (m, 13). ^{d} Nmr (CDCl$_3$), δ 2.5–3.6 (m, 3), 4.33 (m, 1), 5.52 (s, 1), 7.0–8.0 (m, 8).
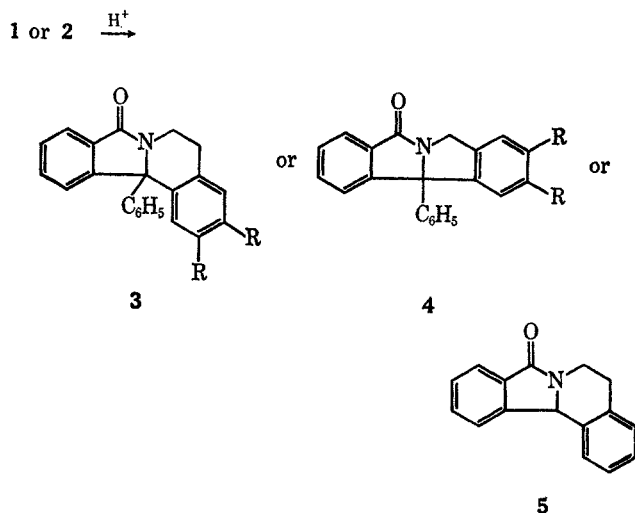
stead of indole. A recent French patent[8] also described cyclizations of a similar nature.

Results and Discussion

Amides of *o*-benzoylbenzoic and phthaladehydic acids exist as cyclic α-alkylol amides (*i.e.*, 1 and 2).[9] From consideration of the work cited above, it seemed likely that examples of this type substituted at nitrogen by aralkyl groups would undergo cyclization by the amidoalkylation process. These 3-hydroxyphthalimidines are easily obtained by treatment of the acid with thionyl chloride followed by the primary amine in triethylamine.[9] Those prepared for the present work are listed in Table I.

Acid-catalyzed cyclization of most of these hydroxyphthalimidines occurred as expected to give the corresponding lactams 3, 4, and 5. See Scheme II. The best conditions were found by trial and error. See Table II. All gave good yields except 1e, 1g, and 2a. Nmr spectra of 3, 4, and 5 clearly showed the loss of one aromatic proton and of an OH proton. Ir spectra

(8) W. Houlihan and R. Manning, French Patent 1,490,023 (1966).

(9) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959). Ir spectra of our amides show C=O at 1675 and OH at 3575 and 3300 cm^{-1}.

SCHEME II

1 or 2 $\xrightarrow{\text{H}^+}$

showed no OH and showed a carbonyl band at 1675 cm^{-1} for 3 and 5 and 1690 for 4. Only tars were obtained from 1e and 2a under a variety of conditions, and 1g gave only tar or starting material.

Secondary amides (*i.e.*, 7–9) derived from 3-benzoylpropionic and levulinic acids do not usually exist

TABLE III
KETO AMIDES

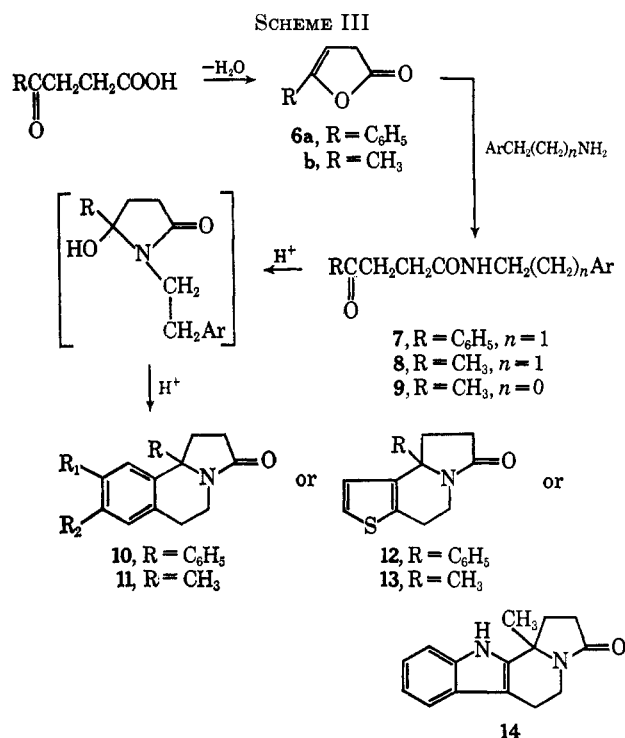| No. | Ar | Mp, °C | Yield, % | Formula | Anal., % | | | | | |
					C Calcd	C Found	H Calcd	H Found	N Calcd	N Found
7a	C_6H_5	98–99	83	$C_{18}H_{19}NO_2$	76.84	76.77	6.81	6.96	4.98	5.12
7b	$C_6H_3(OCH_3)_2$-3,4	93–95	78	$C_{20}H_{23}NO_4$	70.36	70.28	6.79	6.97	4.10	4.00
7c	-2-C_4H_3S	84–86	84	$C_{16}H_{17}NO_2S$	66.89	66.66	5.96	5.74	4.87	5.01
8a	C_6H_5	66–68	82	$C_{13}H_{17}NO_2$[a]	71.21	71.26	7.81	7.80	6.39	6.46
8b	$C_6H_3(OCH_3)_2$-3,4	85–87	71	$C_{15}H_{21}NO_4$	64.50	64.53	7.58	7.41	5.01	5.09
8c	C_6H_4Cl-4	87–89	84	$C_{13}H_{16}ClNO_2$	61.61	61.63	6.32	6.35	5.54	5.70
8d	-2-C_4H_3S	45–47	61	$C_{11}H_{15}NO_2S$	58.66	58.64	6.71	6.67	6.22	6.48
8e	-3-indolyl	80–82	54	$C_{15}H_{18}N_2O_2$	69.74	69.55	7.02	7.25	10.84	10.72
9a	C_6H_5	79–81	90	$C_{12}H_{15}NO_2$[b]	70.22	70.26	7.37	7.36	6.82	7.02
9b	$C_6H_3(OCH_3)_2$-3,4	92–94	83	$C_{14}H_{19}NO_4$	63.38	63.26	7.22	7.28	5.28	5.47

[a] Nmr ($CDCl_3$), δ 2.07 (s, 3), 2.08–2.92 (m, 6), 3.36 (q, 2), 6.15 (m, 1, NH), 7.0–7.3 ppm (m, 5). [b] Nmr ($CDCl_3$), δ 2.07 (s, 3), 2.08–2.90 (m, 4), 4.31 (d, 1, J = 5), 6.50 (broad, 1, NH), 7.18 (s, 5); other compounds in this table have similar spectra.

TABLE IV
PYRROLO[2,1-a]ISOQUINOLIN-3-ONES (10, 11), THIENO[2,3-g]INDOLIZIN-6-ONES (12–14),
AND PYRROLO[2,1-a]-β-CARBOLIN-3-ONES

| No. | R_1 | R_2 | Mp, °C | Yield, % | Reacn conditions[a] | Formula | Anal., % | | | | | |
							C Calcd	C Found	H Calcd	H Found	N Calcd	N Found
10a	H	H	87–89	45	A, 100°, 50 min	$C_{18}H_{17}NO$[b]	82.10	82.35	6.51	6.43	5.32	5.43
10b	OCH₃	OCH₃	144–146	82	B, 100°, 1 hr	$C_{20}H_{21}NO_3$	74.28	74.64	6.55	6.53	4.33	4.23
12			140–141	52	B, 100°, 40 min	$C_{16}H_{15}NOS$	71.36	71.52	5.61	5.75	5.20	5.36
11a	H	H	87–89	71	A, 135°, 2 hr	$C_{13}H_{15}NO$[c]	77.58	77.41	7.51	7.43	6.96	7.13
11b	OCH₃	OCH₃	119–121	82	B, 100°, 1 hr	$C_{15}H_{19}NO_3$	68.94	68.69	7.33	7.39	5.36	5.42
11c	H	Cl	121–123	84	A, 135°, 2 hr	$C_{13}H_{14}ClNO$	63.65	63.92	5.75	5.77	5.71	5.72
13			131–133	68	B, 100°, 30 min	$C_{11}H_{13}NOS$	63.76	63.95	6.32	6.36	6.76	6.65
14			262–265[d]	87	C, 60°, 4 hr	$C_{15}H_{16}N_2O$						

[a] A, Polyphosphoric acid; B, 85% phosphoric acid; C, 2% hydrogen chloride in methanol. [b] Nmr ($CDCl_3$), δ 2.35–3.30 (m, 7), 4.40 (m, 1), 7.08–7.65 ppm (m, 9). [c] Nmr ($CDCl_3$), δ 1.50 (s, 3), 2.0–3.3 (m, 7), 4.25 (m, 1), 7.0–7.3 (m, 4); other compounds in this table have similar spectra. [d] Mp 264–266°: S. Wawzonek and D. Nordstrom, *J. Med. Chem.*, **8**, 265 (1965).

in the cyclized tautomeric forms (*e.g.*, **15**).[10] Even so, it was of interest to determine whether *double* cyclization of such aralkyl amides could be effected to give indolizine derivatives fused to only one aromatic ring. Success was readily achieved by Scheme III.

SCHEME III

6a, R = C_6H_5
b, R = CH_3

7, R = C_6H_5, n = 1
8, R = CH_3, n = 1
9, R = CH_3, n = 0

10, R = C_6H_5
11, R = CH_3

12, R = C_6H_5
13, R = CH_3

14

15

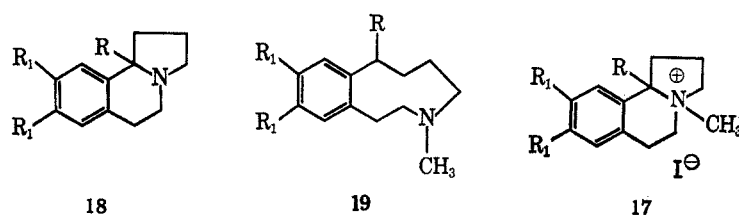(10) N. Cromwell and K. Cook, *J. Amer. Chem. Soc.*, **80**, 4573 (1953).

The keto amides could not be prepared directly from the keto acids by the thionyl chloride method. However, the amines reacted readily with their corresponding dehydration products, 5-methyl- and 5-phenyl-2,3-dihydrofuran-2-one (**6**), to give the keto amides **7**, **8**, and **9**.' Infrared spectra showed that the amides prepared in this manner existed in the open-chain form when dissolved in chloroform. Carbonyl bands in the infrared were 1715 cm⁻¹ and 1660 for **8** and **9** and 1665 (broad) for **7**. Results are summarized in Table III.

The keto amides from arylethylamines underwent the double cyclization in good yield to give the benzo- and thieno-fused indolizines. This is the first reported example of the thieno[2,3-g]indolizine (**12** and **13**) ring system. Again the best conditions were found by trial and error. Results of the ir (carbonyl frequency at 1675 cm⁻¹) and nmr spectra and of the elemental analyses clearly showed that cyclization into the aromatic ring had taken place. The keto amides derived from the benzylamines **9a** and **9b** did not cyclize even under forcing conditions. Under the same conditions that **8a** gave **11a**, **9a** gave the amido alcohol **15**.
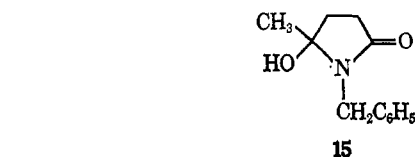
This compound does not exist in equilibrium with **9a** in chloroform as shown by nmr and ir spectra. Its isolation suggests, however, that α-alkylol amides
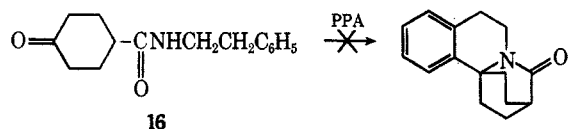
TABLE V

AMINES AND QUATERNARY SALTS

18   19   17

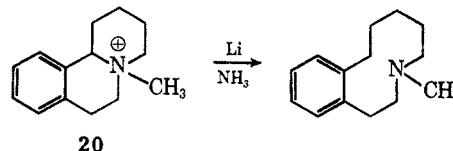| No. | R, R₁ | Mp, °C | Bp (mm), °C | Yield, % | Formula | Anal., % | | | | | |
						C Calcd	C Found	H Calcd	H Found	N Calcd	N Found
18a	CH₃, H		78–82 (0.1)	90	C₁₃H₁₇N[a]	83.37	83.60	9.15	9.07	7.48	7.30
17a	CH₃, H	175–178		98	C₁₄H₂₀IN	51.00	50.79	6.13	6.08	4.25	4.31
18b	C₆H₅, H		140–145 (0.3)	89	C₁₈H₁₉N[b]	86.70	86.40	7.68	7.43	5.62	6.29
17b	C₆H₅, H[c]	83–85		96	C₁₉H₂₂IN	58.65	58.69	6.72	6.96	3.13	3.16
18c	C₆H₅, OCH₃	94–95		79	C₂₀H₂₃NO₂	77.64	77.56	7.49	7.30	4.53	4.53
17c	C₆H₅, OCH₃	245–248		97	C₂₁H₂₆INO₂	55.90	55.98	5.82	5.83	3.11	3.24
19a	CH₃, H[d]		75–77 (0.1)	40	C₁₄H₂₁N[e]	82.70	82.67	10.41	10.35	6.89	7.08
19b	C₆H₅, H	107–109		92	C₁₉H₂₃N[f]	85.99	85.76	8.74	8.59	5.28	5.36
19c	C₆H₅, OCH₃[c]	235–237		90	C₂₁H₂₈ClNO₂	69.70	69.57	7.80	7.92	3.87	3.68

[a] Nmr (CDCl₃), δ 1.28 (s, 3), 1.5–3.2 (m, 10), 6.85–7.15 ppm (m, 4).   [b] Nmr (CDCl₃), δ 1.65–3.25 (m, 10), δ 7.0–7.5 (m, 9).   [c] Contains 1 mol of 2-propanol of crystallization.   [d] Obtained as a mixture with 21, purified by glpc.   [e] Nmr (CDCl₃), δ 1.25 (d, 3, $J = 7$), 1.2–3.2 (m, 10), 2.37 (s, 3), 4.08 (m, 1), 7.05–7.25 (m, 4).   [f] Nmr (CDCl₃), δ 1.0–1.5 (m, 2), 1.9–3.5 (m, 8), 2.37 (s, 3), 5.65 (t, 1, $J = 8$), 6.8–7.5 (m, 9).

of this type (or more likely their protonated forms) are intermediates in the double cyclization of the higher homologs. These results are summarized in Table IV.

An attempt was made to cyclize the keto amide 16, but only polymeric material resulted.
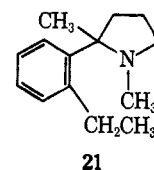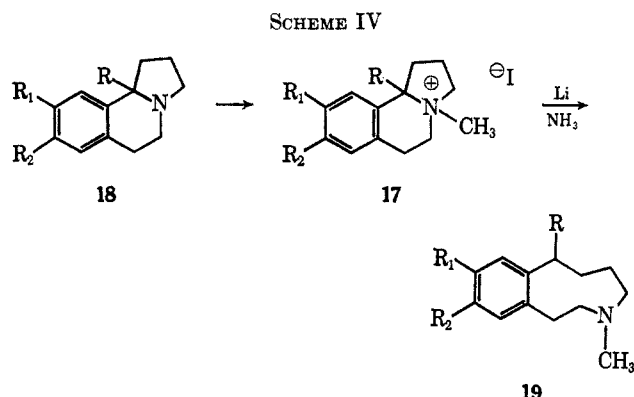

16

Reduction of the lactams of Table IV with lithium aluminum hydride gave the corresponding heterocyclic tertiary amines. The results are summarized in Table V.

The synthetic utility of these reactions was extended further to the preparation of nine-membered ring amines of type 19. The few reported[11–13] syntheses of these benzazonines involve alkaloid degradations. The sequence given in Scheme IV was used in the present work.

SCHEME IV

18   17

19

Cleavage of quaternary heterocyclic ammonium salts to give medium rings has been studied in the indole alkaloid field[14,15] and recently was applied to benzoquinolizidines (20) by Herbst[16a] and Yardley.[16b]

20

In the present work it was found that the cleavage reaction occurred in nearly quantitative yield when an angular phenyl group was present as in 17 (R = C₆H₅, R₁ = H, OCH₃). However with an angular methyl group (17, R = CH₃, R₁ = H), the desired benzazonine was obtained as part of a mixture of isomers (40% 19) which could only be separated by preparative glpc. The other isomer which was the major component has been tentatively indentified as 21, and would result from a Hoffman elimination followed by

21

reduction of the resulting olefin. This contrasts with the work of Herbst who cleaved 20 in good yield. However, in their reaction, a secondary carbanion in a ten-membered ring is the intermediate, whereas in our case, the less favored tertiary carbanion in a nine-membered ring is the intermediate. With an angular phenyl group, the more stable benzhydryl carbanion

(11) J. Weinstock and V. Boekelheide, *J. Amer. Chem. Soc.*, **75**, 2546 (1953).
(12) J. Godfrey, D. S. Tarbell, and V. Boekelheide, *ibid.*, **77**, 3343 (1955).
(13) K. Wada, S. Marumo, and K. Manakata, *Tetrahedron Lett.*, **5**, 179 (1966).

(14) L. Dolby and D. L. Booth, *J. Org. Chem.*, **30**, 1550 (1965); J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Amer. Chem. Soc.*, **88**, 3656 (1966); J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966).
(15) E. Wenkert, S. Garratt, and K. Dave,*Can. J. Chem.*, **42**, 489 (1964).
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intermediate presumably accounts for the excellent yields of nine-membered ring product.

In conclusion, the intramolecular amidoalkylation reaction is a convenient method of synthesizing tertiary heterocyclic amides and amines, especially with angular substituents. It compares favorably with the known isoquinoline-forming reactions,[17] and in certain cases can lead to fused isoindolines (*e.g.*, 4) which are difficult to prepare by other means.

Experimental Section

All compounds had ir and nmr spectra consistent with their structure. A rotary evaporator was used to concentrate all solvents (other than ether) under reduced pressure. All starting materials are either commercially available or described in the literature.

Cyclic Amides of *o*-Benzoylbenzoic Acid and Phthalaldehydic Acids (1 and 2).—The acid was dissolved in thionyl chloride (4 ml/g of acid) at room temperature and allowed to stand for 3 hr. The solution was then refluxed for 15 min and concentrated under reduced pressure. Chloroform was added to the residue and then removed by distillation under vacuum. This was repeated twice more in order to eliminate all the thionyl chloride. The final solution in chloroform (5 ml/g of acid) was cooled while 1.25 equiv of triethylamine was added all at once. Then 1.0 equiv of primary amine was added over a 10–15-min period while cooling in an ice bath. The solution was left at room temperature overnight and then extracted with dilute hydrochloric acid. The chloroform solution was dried over anhydrous potassium carbonate and concentrated; the residue was recrystallized from chloroform–ether mixtures. Data for the individual compounds are in Table I.

5-Phenyl-2,3-dihydrofuran-2-one (6a).—3-Benzoylpropionic acid (150 g) was mixed with 600 ml of acetic anhydride and kept at 100–115° for 3.5 hr. The red solution was concentrated to dryness, and the residue was recrystallized twice from chloroform–ether giving 90.6 g (67.1% yield) of tan plates, mp 91–92° (lit.[18] mp 92–93°).

Amides of Levulinic and 3-Benzoylpropionic Acid (7–9).—To a 15% solution of α-angelicalactone (6b)[19] or lactone 6a in chloroform, an equivalent amount of primary amine was added at once with stirring and cooling. When 6a was used, the color of the solution turned black, but lightened gradually. The solution was kept at room temperature for 4 hr and then was concentrated; the residue was crystallized from chloroform–ether mixtures. For yields and other data for the individual compounds see Table III.

Cyclizations of α-Alkylol Amides and Keto Amides.—The keto amide or cyclic α-alkylol amide was mixed with a volume of solvent (see Tables II and IV) equal to ten times its weight and kept at the temperature for the length of time indicated in the tables. Then the solution was poured into crushed ice and chloroform and salted out with a volume of 50% sodium hydroxide equal to one-fifth of the volume of the solvent. The chloroform was dried over potassium carbonate and concentrated, and the residue was crystallized from ethanol or chloroform–ether mixtures.

N-Benzyl-5-methyl-5-hydroxypyrrolidone (15).—N-Benzyl levulinamide (9a), (5.00 g) was heated at 140° for 2 hr in 50 ml of polyphosphoric acid and the solution was worked up as indicated in the foregoing procedure to give 2.92 g (59%) of crystals, mp 64–66°. Ir and nmr spectra indicated complete conversion to the cyclic amido alcohol 15.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.05; H, 7.47; N, 6.78.

Reduction of Cyclic Amides to Amines.—To a 7% solution of the amide in dry tetrahydrofuran, an amount of lithium aluminum hydride equal to 0.4 times the weight of the amide was added in portions, while cooling in an ice bath and under a

nitrogen atmosphere. The mixture was refluxed for 4 hr and then cooled; while being stirred under nitrogen, a volume of water equal to that of the weight of the starting amide was added very slowly. After being stirred for 25 min, a volume of 50% sodium hydroxide equal to half that of the water used, was added dropwise. After 20 min, the aluminum salts were removed by filtration and washed with tetrahydrofuran. The organic phase was concentrated and either crystallized or distilled to give the products listed in Table V.

Preparation of Methiodides (17).—A 10% solution of the amine in chloroform was treated with 2 equiv of methyl iodide and left overnight at room temperature. The solution was then concentrated, and the residue was crystallized from isopropyl alcohol (to yield 17b and 17c) or chloroform–benzene (to yield 17a).

Preparation of Benzazonines (19a–c).—To a 2–5% suspension of the methiodide in liquid ammonia (at −33°) under an atmosphere of nitrogen, there was added 1 equiv of isopropyl alcohol (17b already contained isopropyl alcohol of crystallization and no additional proton donor was needed). To the stirred solution freshly scraped lithium wire was added in portions until a blue color persisted for 100 sec. About 1.2 equiv of lithium were added. The blue color was discharged with water, and then the ammonia was distilled on a water bath and replaced with ether. From the ether phase there was obtained a residue which was either crystallized (19b), distilled (19a), or converted into the hydrochloride with hydrogen chloride in isopropyl alcohol (19c).

N-(2-Phenylethyl)-4-cyclohexanone Carboxamide (16).—Ethyl cyclohexanol-4-carboxylate[20] (42.0 g), 2-phenylethylamine (100 g), ammonium chloride (3.0 g), and xylene (100 ml) were refluxed for 24 hr. Then 100 ml of solvent was distilled at atmospheric pressure and replaced with 20 g of 2-phenylethylamine and 60 ml of xylene. This solution was refluxed for another 16 hr. The solution was concentrated, and the residue was crystallized from chloroform–ether giving 43.5 g of a mixute of *cis* and *trans* isomers of the amido alcohol, mp 110–130°. This was suspended in 1 l. of acetone and treated slowly at room temperature with a solution of 17 g of chromium trioxide in 37 ml of water plus 15 ml of concentrated sulfuric acid. After addition was complete, the green solution was stirred for 0.5 hr and then treated with 10 ml of isopropyl alcohol. The acetone was decanted from the settled residue and then removed by distillation, and the residue left was treated with chloroform and an aqueous sodium bicarbonate solution. The original green residue also was extracted with chloroform. The combined chloroform extracts were dried over potassium carbonate and concentrated to give 24.9 g (42%) of 16, mp 134–136° (from chloroform–ether).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.87; N, 5.71. Found: C, 72.61; H, 7.72; N, 5.55.

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